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Study of Impact of Adverse Drug Reaction of Chemotherapy on Treatment Outcome, Overall Morbidity and Mortality of Oral Cavity Squamous Cell Carcinoma: A Prospective Longitudinal Study

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Abstract

Evaluation of impact of adverse drug reactions of chemotherapy for treatment of oral cavity squamous cell carcinoma. A prospective longitudinal study was conducted by enrolling all newly diagnosed patients of oral cavity squamous cell carcinoma (OCSCC), who were to receive chemotherapy. After getting informed written consent, according to clinical criteria, patients were divided into Concurrent Chemo-Radiation (CTRT) and Neo-Adjuvant Chemotherapy (NACT) group. Patients' baseline demographic, clinical and hematological profiles were noted during enrollment and they were followed up for development of any adverse drug reaction (ADR) by analysis of history and investigations. Causality of ADRs were assessed and the impact of ADR was evaluated by the treatment outcome in the form of severity, mortality, morbidity and loss to follow up of the standard treatment. In this observational study, out of total 67 eligible patients, 63 patients consented to participate in the study, while total 41 patients completed the treatment. There were total 5 (7.93%) deaths during follow up, while 22 (34.92%) patients were noncompliant with the treatment. All the patients had developed one or more ADRs, which further deteriorated treatment outcome. On causality assessment, 73% adverse drug reactions were classified under possible group. Moreover, majority of ADRs were moderate in severity and half of the ADRs were not preventable. In short, in spite of giving prophylactic measure during chemotherapy of OCSCC, the outcome of treatment of OCSCC remains poor due to the disease itself and treatment related ADRs.

Keywords: Adverse drug reaction, causality assessment, chemotherapy, concurrent chemo-radiation, neo-adjuvant chemotherapy, oral cavity squamous cell carcinoma.

Introduction

Carcinoma remains the leading cause of morbidity and mortality all over the world with its relative position varies with age and sex[1]. In the year 2010, analysis of prevalence of cancer in developing country like India had shown that there was estimated total cases of cancer to be around 2.5 million, with over 8,00,000 new cases and 5,50,000 deaths occurring each year. Overall, cancers of lung, oesophagus, stomach, oral and pharyngeal cancers, mostly affect men. On the other hand, cervical and breast cancers are most common in women[2].

On analysis of the most common cancers in the world, oropharyngeal carcinoma is ranked at the sixth place and oral cavity squamous cell carcinoma (OCSCC) incorporates 90 % of all cases of oropharyngeal cancer[1].

The treatment of OCSCC involves surgical resection and adjuvant radiotherapy and/or chemotherapy. In spite of advances in diagnosis and treatment, impact on a patient's treatment outcome is determined by disfigurement caused by not only the disease itself but also due to adverse reactions of difficult treatment. On the other hand, oral cancer represents a major health problem in India, which constitutes up to 40% of all cancers and is the most prevalent cancer in males and the third most prevalent cancer in females[3,4].

In spite of such heavy burden of disease and their adverse drug reactions, no such type of study has yet been carried out in patients of OCSCC in India[3,5]. So, this study was aimed to evaluate impact of adverse drug reactions (ADR) in patient of Oral Squamous Cell Carcinoma (OCSCC) receiving chemotherapy.

Material and Methods

Ethical permission: Before starting this study, permission of ethical committee was taken from the Scientific and Ethical Review Committee (SERC) of Medical College, Baroda.

Site of the study: This study was conducted in the Radiotherapy Department of the tertiary care teaching hospital of Baroda, India.

Study design: In this prospective longitudinal study, patients were followed up to track adverse events as they occur. As this

was out patient department based observational study of approved drugs, blinding or randomization was not done.

Study population: All the patients of OCSCC, attending the outpatient department, who satisfied inclusion- exclusion criteria, were enrolled in the study before starting Concurrent Chemo-Radiation or Neo-Adjuvant Chemotherapy.

Inclusion Criteria: All newly diagnosed patients who were to receive chemotherapy with or without radiation therapy for histopathologically proven OCSCC, with age above 18 years, who agreed to give informed-written consent to participate voluntarily, were enrolled in the study.

Exclusion criteria: Following patients were excluded during enrolment procedure of this study: i. unwillingness to participate the study ii. taking treatment at other centers iii. diagnosed case of psychiatric illness or cognitive impairment iv. pregnant or nursing mother v. suffering from terminal illness.

Sample size: In India, oral cavity cancer constitutes 29.54% among all malignant biopsies and 95% oral cavity carcinoma with squamous cell type[6]. Considering previous records of radiotherapy department, average 15-20 new patients of OCSCC were receiving chemotherapy every month, after using this information for calculating sample size at 5% confidence interval with 95% confidence level, total estimated minimum sample size for this study was 30.

Treatment protocol: The standard treatment for patients with OCSCC is Concurrent Chemo radiation -CTRT followed by definitive surgery[7,8], while NACT is either given with the intent of achieving: i. surgical resection of extensive soft tissue disease, oropharyngeal involvement, extensive disease with cartilage erosion or ii. organ preservation for bulky disease with inner cartilage erosion, exolaryngeal disease without cartilage erosion or large N3 nodes[9-13].

In CTRT group, patients were treated with 25-30 fractions of 50 - 60 Gray External Beam Radiotherapy for 5-6 weeks, using reducing fields at site of OCSCC with weekly chemotherapy as a radiation sensitizer. For chemotherapy patients were treated with prophylactic *Palonosetron, Dexamethasone, Pheniremine Maleate, Mannitol and Hydration with 500 ml Dextrose Normal Saline (DNS), 5% Dextrose and Ringer's Lactate (RL), followed by Cisplatin 12 mg/m^2 or 5-fluorouracil (5 FU) 600 mg/m^2 every week for six cycles.* The overall evaluation baseline parameter of patients of OCSCC was carried out before starting first cycle of chemotherapy (C0), and patients were again evaluated for development of ADRs every week after completion of each cycle of chemotherapy at the end of C1, C2, C3, C4, C5, C6 [14]. The last evaluation of ADR was done one month after completion of the last cycle of chemotherapy (i.e.C7).

In NACT group, patients were treated with *Palonosetron, Dexamethasone, Pheniremine Maleate, Mannitol and Hydration with 500 ml DNS, 5% Dextrose and RL,* followed by *Neo Adjuvant chemotherapy was given as two (platinum with taxane) or three drugs with Platinum, Taxane with 5-fluorouracil (5 FU) every 3 week regimen with Cisplatin 12 mg/m^2 and Docetaxel as 75 mg/m^2 and 5-FU as 1000 mg/m^2* . Similarly, in this group, baseline characteristics of patients of OCSCC were evaluated before the first cycle of chemotherapy (C0) and patients' ADR was evaluated every third week after completion of each cycle of anticancer drugs (e.g. C1,C2,C3,C4). The last evaluation of ADR was done one month after completion of the last cycle of chemotherapy (i.e. C5)[12, 13].

Data collection and follow up: After enrollment of patients in the study, demographic and clinical data of the patients were recorded at presentation to the outpatient department. According to treatment protocol decided by the consultant, patients were divided in CTRT and NACT groups.

Patients' ADR was evaluated by suspected adverse drug reaction reporting form to the patients at each visit and development of ADRs were evaluated before starting chemotherapy, after completion of each cycle of chemotherapy and one month after completion of full course of treatment. Development of ADRs was evaluated by data obtained from the clinical records of patients and all the data was entered into excel worksheet.

Study period: This study was conducted from January 2013 to September 2013. Patients' recruitment period was for initial three months and they were followed up after each cycle of chemotherapy and one month after completion of full course of chemotherapy.

Causality assessment of adverse drug reactions and adverse events: Causality assessment of all the symptomatic and investigated ADRs were done by World Health Organization's Uppsala Monitoring Centre (WHO-UMC) advised causality assessment scale**[5].**

Moreover, preventability assessment of ADRs were done by using Modified Schumock and Thornton scale **[15]**, while the severity of ADRs were analyzed by Modified Hartwig and Siegel Scale**[16]**.

Results and Discussion

In this prospective longitudinal study, evaluation of adverse drug reactions of chemotherapy for OCSCC was done during each visit of patients taking anti- cancer drugs by using suspected adverse drug reaction reporting form.

According to treatment protocol, patients were divided into Concurrent Chemo - Radiation (CTRT) and Neo-Adjuvant Chemotherapy (NACT) groups and adverse drug reactions were assessed by evaluation of history and laboratory investigations after each cycle of chemotherapy followed by one month after

completion of full course of chemotherapy.

Analysis of compliance to treatment: In CTRT group, according to inclusion and exclusion criteria, 38 (56.72%) patients were eligible, out of them 34 (50.75%) had given consent to participate in the study. On the other hand, total 18 (26.87%) patients could complete full course of chemotherapy and one month's follow up thereafter, while total 17 (25.37%) patients were excluded due to incomplete follow up.

In NACT group, according to inclusion and exclusion criteria, 29 (43.28%) patients were eligible, all of them 29 (43.28%) had given consent to participate in the study. Total 11 (16.42%) patients were excluded due to incomplete follow up or inability to complete 4 cycles of chemotherapy. 2 (2.99%) patients died during the study period. Total 18 (26.87%) patients could complete 6 cycles of chemotherapy and follow up after one month of the last cycle of chemotherapy.

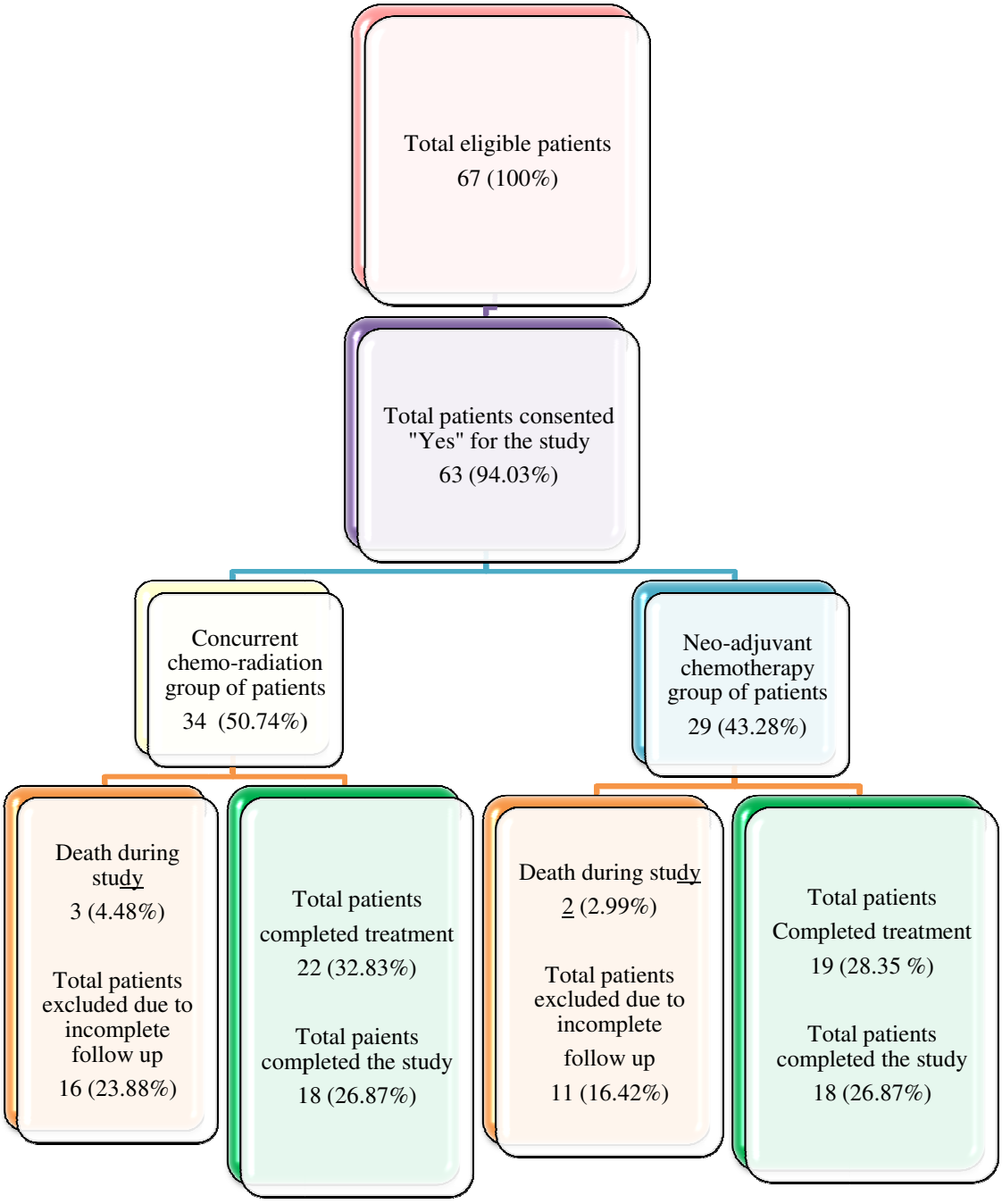

Figure-1
Enrollment of patients as per inclusion and exclusion criteria

Enrolment status: Considering all patients, 67 patients were eligible, out of them 63 (94.03%) had given consent to participate in the study. Total 28 (41.79%) patients were excluded due to incomplete follow up or inability to complete the full course of chemotherapy and among them 5 (7.46%) patients died during the study period. Total 36 (53.73%) patients could complete chemotherapy treatment and follow up after one month of the last cycle of chemotherapy as shown in figure-1.

Demographic features: As shown in table-1, oral cavity squamous cell carcinoma was seen predominantly among male farm workers, who were married and they presented with OCSCC during the fourth or fifth decade of life.

Stage of OCSCC: As shown in table-2, majority of patients reported for the chemotherapy during the advanced TNM stage of oral cavity squamous cell carcinoma.

Site of OCSCC: On analysis of the histopathological report of oral cavity squamous cell carcinoma, as shown in figure-2, commonly observed site in descending order was tongue followed by buccal mucosa, palate, alveolus, retro molar trigone and anterior faucial pillar.

Addiction history: Out of 36 patients, 29 (80.56%) patients had one or more addictions. In other words, total 16(44.44%) patients had a history of betel nut chewing, 15(41.67%) patients reported their history of smoking and 4(11.11%) were having history of alcohol consumption. Overall, total 4 (11.11%) patients had history of alcohol consumption and smoking, while 2 (5.56%) patients had history of smoking and betel nut chewing.

Adverse drug reactions: In this study, a common terminology criterion for adverse event was used for detection of adverse event during the study period. After eliciting history, patients had noted various adverse drug reactions like nausea, vomiting, anorexia, diarrhoea, fatigue, dyspnoea, insomnia, weakness, oral mucositis, dysphagia for solid, difficulty in speaking, weight loss and dryness of mouth. On the other hand, analysis of investigations, adverse events like anaemia, neutropenia, myelosuppression, altered renal function or liver function was detected as shown in table 3 to 6.

Table-1
Demographic features of patients with oral cavity squamous cell carcinoma

Criteria	Concurrent chemo-radiation group (N=18)	Neo-adjuvant chemotherapy group (N=18)	Total (N=36)
Age (Years) (Mean ± SD)	48 ± 10	47.78 ± 10.94	47.89 ± 10.48
Male	13 (72.22%)	13 (72.22%)	26 (72.22%)
Female	5 (27.78%)	5 (27.78%)	10 (27.78%)
Weight (Kg) (Mean ± SD)	49.33 ± 11	47.44 ± 8.16	48.39 ± 9.82
Height (Cm) (Mean ± SD)	158 ± 11	161.94 ± 10.51	160.19 ± 10.73
BMI (Kg/m2) (Mean ± SD)	19.62 ± 3.69	18.07 ± 2.63	18.85 ± 3.25
Married	18 (100%)	17 (94.44%)	35 (97.22%)
Unmarried	0 (0%)	1 (5.56%)	1 (2.78%)

N = Number of patients of oral cavity squamous cell carcinoma; BMI = Body mass index; SD = Standard deviation

Table-2
Patients' TNM stage of oral cavity squamous cell carcinoma

TNM* stage of oral cavity squamous cell carcinoma	Number of patients in Concurrent chemo-radiation group (N=18)	Number of patients in Neo-adjuvant chemotherapy group (N=18)	Total number of patients (N=36)
I	3 (16.67%)	2 (11.11%)	5 (13.89%)
II	6 (33.33%)	5 (27.78%)	11 (30.56%)
III	7 (38.89%)	9 (50.00%)	16 (44.44%)
IV	2 (11.11%)	2 (11.11%)	4 (11.11%)

N = Number of patients of oral cavity squamous cell carcinoma; TNM = Tumour, node and metastasis; *TNM staging of American Joint Committee on Cancer (AJCC), Chicago, Illinois.

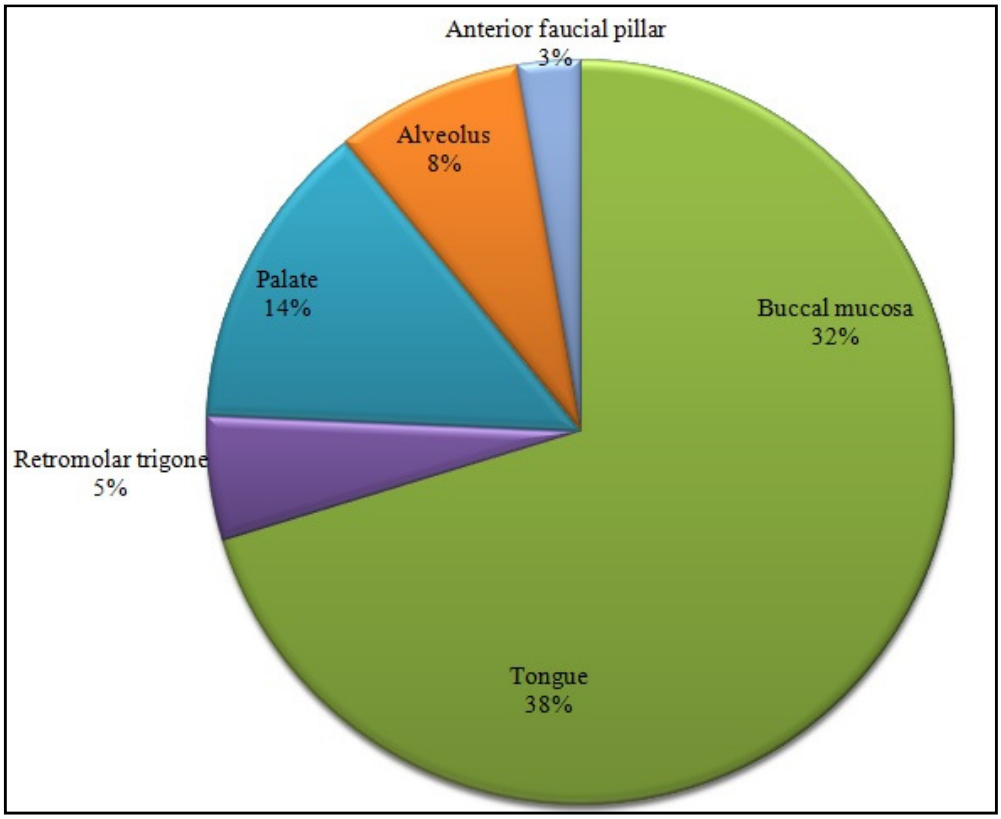

Figure-2
Site of oral cavity squamous cell carcinoma among all patients (N=36)

Table-3
Causality assessment of symptomatic adverse drug reactions in concurrent chemo-radiation group

Symptoms (N=18)	**Total no of patients with adverse drug reactions (N=18)**	**Total adverse drug reactions**	**Certain**	**Probable**	**Possible**	**Unlikely**	**Conditional**	**Unclassifiable**
Dyspnoea	2 (11.11%)	10	00	00	2	8	00	00
Insomnia	15 (83.33%)	59	00	00	41	00	00	18
Weakness	12 (66.67%)	59	00	00	43	7	00	9
Anorexia	11 (61.11%)	48	00	00	41	1	00	6
Nausea	17 (94.44%)	61	00	00	56	00	00	5
Vomiting	16 (88.89%)	48	00	00	43	00	00	5
Diarrhoea	6 (33.33%)	7	00	00	5	2	00	00
Fatigue on daily work	14 (77.78%)	63	00	00	54	00	2	7
Oral mucositis	13 (72.22%)	62	00	00	51	6	00	5
Dysphagia for solid	13 (72.22%)	85	00	00	00	77	00	8
Difficulty in speaking	15 (83.33%)	97	00	00	82	10	00	5
Weight loss	10 (55.56%)	33	00	00	26	7	00	00
Dryness of mouth	18 (100.00%)	101	00	00	101	00	00	00
Total		733	00	00	545	118	2	68

Table-4
Causality assessment of investigated adverse drug reactions of concurrent chemo-radiation group

Investigated Finding (N=18)	**Total no of patients with adverse drug reactions (N=18)**	**Total no of adverse drug reactions**	**Number of adverse drug reactions**	**Causality assessment**	**Suspected medication/s**
Gr I Anaemia Hb <10	7 (38.89%)	16	16	Possible	Cisplatin, 5-fluorouracil
Absolute neutrophil count < 2000	2 (11.11%)	2	2	Probable	Cisplatin
Platelets < 150000	8 (44.44%)	9	9	Possible	Cisplatin, Cefadroxil, Amoxicillin, Ranitidine, Paracetamol, Ibuprofen,
Myelosuppression	1 (5.56%)	1	1	Probable	Cisplatin
Urea > 40	7 (38.89%)	16	3	Probable	Cisplatin
			13	Possible	Cisplatin, Cefadroxil
Total Bilirubin > 1	1 (5.56%)	1	1	Probable	Cisplatin
SGPT > 40 (Male)	5 (27.78%)	9	9	Possible	Cisplatin, Diclofenac Sodium
SGPT > 28 (Female)	1 (5.56%)	1	1	Possible	Cisplatin, Diclofenac Sodium

SGPT = Serum glutamate pyruvate transaminase; SGOT = Serum glutamic oxaloacetic transaminase; Hb = Hemogobin

Table-5
Causality assessment of symptomatic adverse drug reactions of neo-adjuvant chemotherapy group

Symptom (N=18)	**Patients (N=18)**	**Total no of patients with adverse drug reactions (N=18)**	**Certain**	**Probable**	**Possible**	**Unlikely**	**Conditional**	**Unclassifiable**
Dyspnoea	2(11.11%)	10	00	00	8	2	00	00
Insomnia	17(94.44%)	59	00	00	41	00	00	18
Weakness	12(66.67%)	38	00	00	30	5	00	3
Anorexia	9(50.00%)	28	00	00	24	3	00	1
Nausea	17(94.44%)	47	00	20	26	1	00	00
Vomiting	17(94.44%)	25	00	19	5	1	00	00
Fatigue	13(72.22%)	27	00	00	19	3	00	5
Diarrhoea	4(22.22%)	5	00	00	4	00	00	1
Oral mucositis	16(88.89%)	44	00	00	23	21	00	00
Dysphagia for solid	5((27.75%)	18	00	00	18	00	00	00
Difficulty in speaking	10(55.56%)	38	00	00	26	12	00	00
Weight loss	8(44.44%)	29	00	00	25	4	00	00
Dryness of mouth	3(16.67%)	9	00	00	9	00	00	00
Total		377	00	39	258	52	00	28

Table-6
Causality assessment of investigated adverse drug reactions of neo-adjuvant chemotherapy group

Investigated Finding (N=18)	Total no of patients with adverse drug reactions	Total adverse drug reactions	Number of. adverse drug reactions	Causality assessment	Suspected medication/s
Gr I Anaemia Hb <10	7(38.89%)	18	3	Probable	Cisplatin
			8	Possible	Cisplatin, Docetaxel
			7	Unclassifiable	Follow up investigation required
Absolute neutrophil count < 2000	1(5.56%)	1	1	Possible	5-fluorouracil, Cisplatin
Platelets < 150000	3(16.67%)	3	3	Possible	Cisplatin, 5-fluorouracil, Amoxicillin, Famotidine
Urea > 40	7(38.89%)	10	2	Probable	Cisplatin
			7	Possible	Cisplatin, Cefadroxil, Methotrexate
			1	Unclassifiable	Follow up investigation required
S. Creatinine > 1.4	2(11.11%)	2	1	Possible	Cisplatin, Cefadroxil
			1	Unclassifiable	Follow up investigation required
Total Bilirubin > 1	2(11.11%)	3	3	Possible	Cisplatin, Diclofenac Sodium
SGPT > 40 (Male)	2(11.11%)	2	2	Probable	Cisplatin
SGPT > 28 (Female)	1(5.56%)	1	1	Unclassifiable	Follow up investigation required

SGPT = Serum glutamate pyruvate transaminase; SGOT = Serum glutamic oxaloacetic transaminase; Hb = Hemoglobin

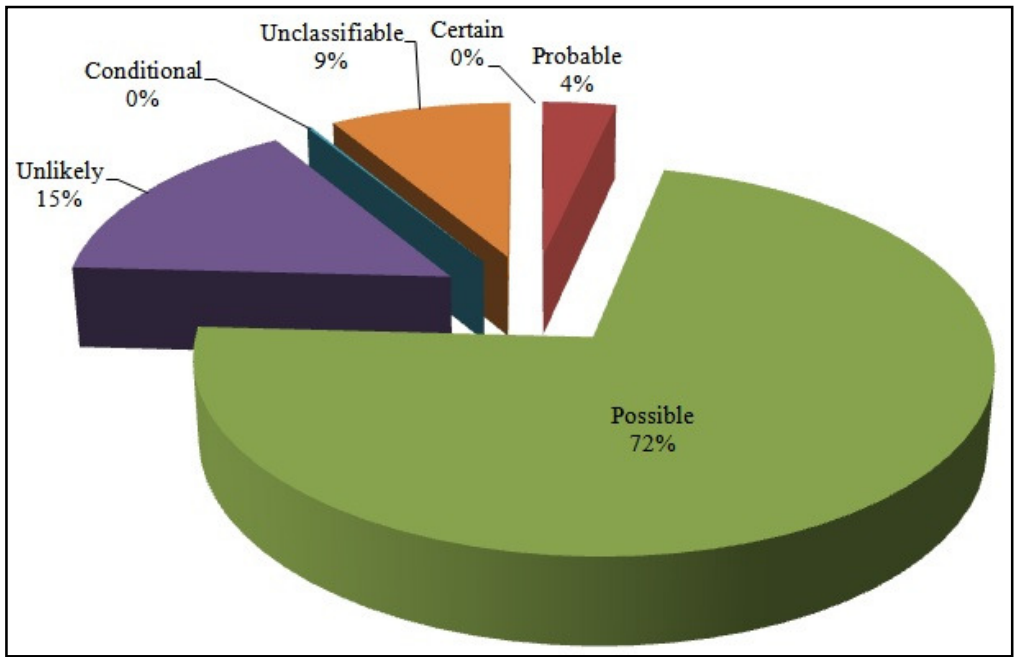

Figure-3
Causality assessment of symptomatic adverse drug reactions of all patients (N=36)

Causality assessment of adverse drug reactions: Overall assessment of *symptomatic* ADRs evaluated by *Causality Assessment Scale of WHO UMC* had shown that, the majority of adverse drug reactions was classified under possible group (72.34%), followed by unlikely (15.31%), unclassifiable group (8.65%) and probable (3.51%) group as shown in figure-3.

Similarly, overall assessment of adverse drug reactions identified by *investigations,* it was concluded that the majority of adverse drug reactions was classified under possible group (73.68%), followed by probable (12.63%) and unclassifiable group (10.53%) as shown in figure-4.

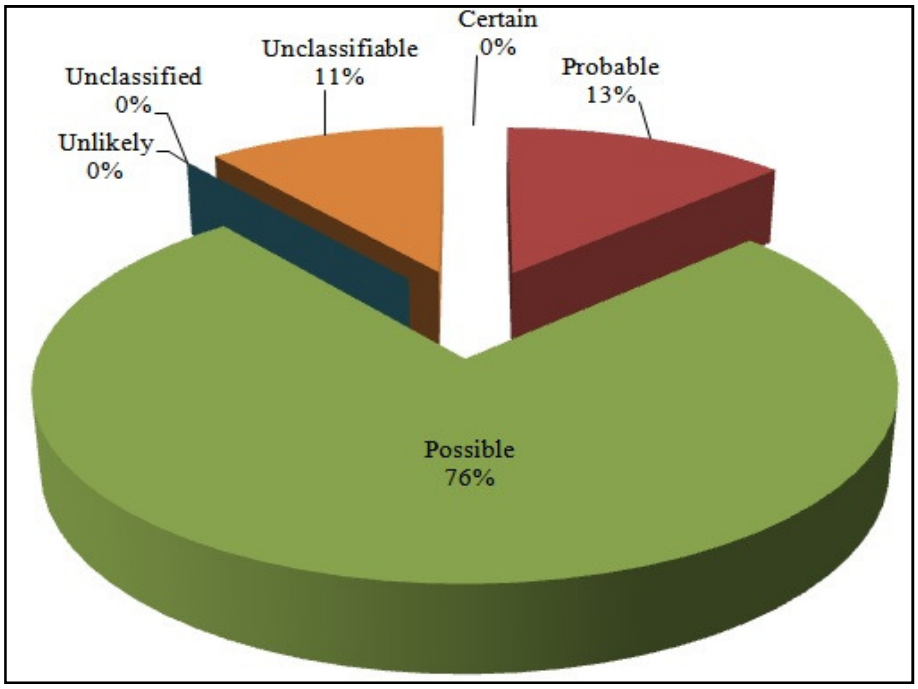

Figure-4
Causality assessment of investigated adverse drug reactions of all patients (N=36)

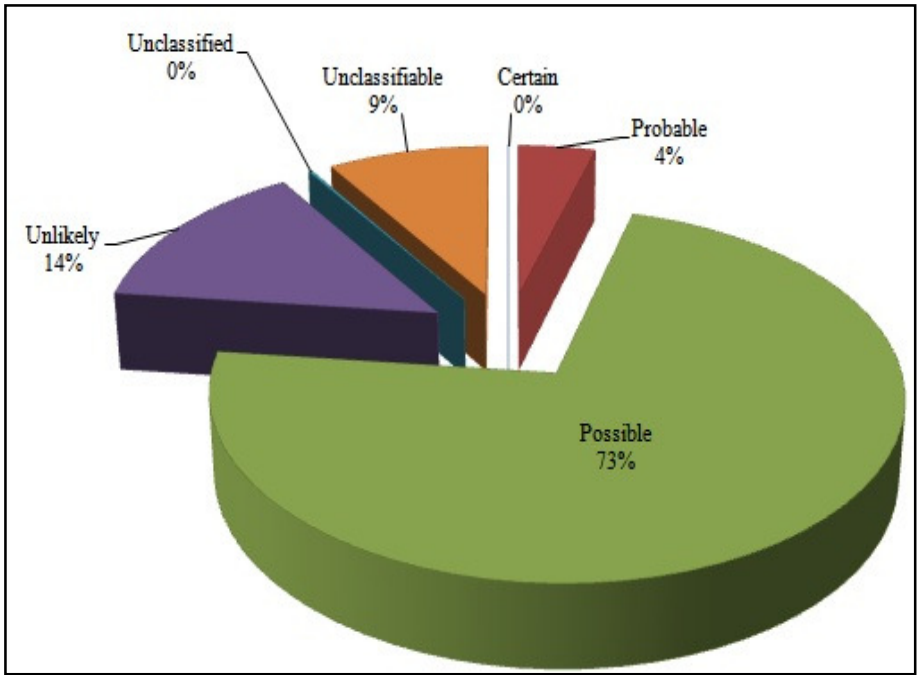

Figure-5
Causality assessment of all adverse drug reactions of all patients (N=36)

In conclusion, an overall analysis of adverse drug reactions, identified by symptoms and investigations by using WHO-UMC causality assessment scale showed that, the majority of adverse drug reactions was classified under possible group (72.45%), followed by in decremented order unlikely (14.11%), unclassifiable (8.79%), probable (4.23%) and unclassified (0.16%) group as shown in figure-5.

Preventability Assessment: On evaluation of preventability chances of ADRs by using the *Scale of Modified Schumock and Thornton*, it was observed that almost half of the ADRs (51.45%) were not preventable, while only 6.47% were definitely preventable. On the other hand 42.08 % were probably preventable as shown in table-7.

Severity Assessment: As shown in table-8, on assessing the level of severity of ADRs by using the *Scale of Modified Hartwig and Siegel*, it was concluded that most of the ADRs reported in the study were of moderate in severity followed by mild and severe.

Discussion: According to WHO, every year, on 31 May, World No Tobacco Day is celebrated to highlight the health risks associated with tobacco consumption and to advocate effective policies to reduce tobacco consumption[17]. In spite of spreading awareness about the harm of tobacco addiction, there is a rise in the number of patients developing cancer of the aero digestive tract. So, this prospective longitudinal study was carried out on all new patients of Oral Cavity Squamous Cell Carcinoma (OCSCC) who were to receive Concurrent Chemo-Radiation (CTRT) or Neo-Adjuvant Chemotherapy (NACT), and they were followed up for development of ADR at the end of each cycle of chemotherapy.

On the whole, this study has shown that patients of OCSCC demonstrated geographical variation according to the age, sex, site and habits of the population and patients were given different chemotherapeutic agents based on age of patient, site and stage of oral cavity cancer, associated comorbid conditions, experience of consultants and availability of drug at government supply.

All the patients enrolled in this study were inhabitant of western India and among all diagnosed cases of OCSCC, the majority of patients presented during the fourth or fifth decade of life and this finding is similar to that observed by Sharma P et al, Mehrota et al and Sankaranarayana et al[5-7].

According to this study, the majority of patients of OCSCC were male, which is in accordance to Indian demographic data suggestive of male predominance for development of oral cancer[18].

In this study, the majority of patients presented with OCSCC of anterior 2/3rd of the tongue, followed by buccal mucosa, these findings are consistent with previous studies showing variation of site of cancer depending on addiction practices[18].

In our study, out of 36 patients, 29 patients had one or more addictions. Smoking, alcohol consumption and betel nut chewing were the most frequently reported addictions among these patients, which support findings of Manuel S et al. and Mehrotra R et al, who found that tobacco chewing or tobacco smoking in the form of "bidi" or "cigarette" were the most prevalent habits in patients with oral cancer[19,20].

Table-7
Preventability assessment of adverse drug reactions by the scale of Schumock and Thornton

Preventability scale	Total number of adverse drug reactions (N=36)	Percentage of adverse drug reactions (100)
Definitely preventable	78	6.47 %
Probably preventable	507	42.08 %
Not preventable	620	51.45 %
Total	1205	100.00 %

Table-8
Severity assessment of adverse drug reactions the scale of Hartwig and Siegel

Severity assessment scale	Number of adverse drug reactions (N = 36)	Percentage of adverse drug reactions (100)
Mild	349	28.96 %
Moderate	808	67.05 %
Severe	48	3.98 %
Total	1205	100.0 %

In this study it was found that, the majority of patients of OCSCC presented during the advanced stage of disease in both the CTRT and NACT group. This finding is similar to Indian patients' clinical profile of oral cavity squamous cell carcinoma[19]. In the same way, the delay in diagnosis of oral squamous cell carcinoma might be correlated to patient delay in looking for medical help[20].

In our study, farm work was the most frequent occupation of patients with OCSCC and similar finding was observed in the previous study, which can be explained as farmers are more indulged in tobacco addiction because nicotine acts as the stimulant for them[21].

Overall, treatment of patients of oral cavity squamous cell carcinoma with anticancer drugs and radiotherapy was associated with various adverse drug reactions which show adverse impact on treatment outcome. According to finding of this study, all patients had developed one or more adverse drug reactions, which suggest a high incidence of chemotherapeutic agent induced adverse outcome, similar finding was observed in another study, which showed that most of the patients receiving cancer chemotherapy developed ADRs and most common ADRs were nausea and vomiting followed by neutropenia due to chemotherapy[22].

In short, patients of OCSCC had developed various symptomatic adverse drug reactions like dyspnoea, insomnia, weakness, nausea, vomiting, fatigue, oral mucositis, dysphagia for solid food, and difficulty in speaking, weight loss and dryness of mouth which might be associated with one or more anticancer drug, supportive medications or radiotherapy. Moreover, development and persistence of weight loss, weakness and fatigue can be related to chemotherapy induced anaemia, neutropenia, thrombocytopenia, myelosuppression, altered renal function or altered liver function. These findings are also supported by another study showing that chemotherapeutic agents produces ADRs like nausea, vomiting, myelosuppression or mucositis[23].

Causality assessment of ADRs: Overall causality assessment of symptomatic and investigated ADRs/AEs was done by WHO-UMC causality assessment scale, which showed that the majority of adverse drug reactions were classified under possible group, followed by in decremented order unlikely, unclassifiable, probable and unclassified group. Similar findings were seen in previous studies showing predominance of possible adverse reactions[24,25].

Clinical correlation of ADRs: Overall development of various symptoms and signs can be disease progression or adverse drug reactions with drugs used for treatment. Here, development of insomnia can be related to radiation induced dryness of mouth, injection of dexamethasone before starting chemotherapy or its' association with disease due to pain over site of oral cavity cancer. Complaint of diarrhea, nausea or vomiting can be due to radiotherapy, cisplatin, methotrexate, metronidazole, mannitol, carboplatin, metronidazole, iron, omeprazole, ciprofloxacin or azitromycin.

Similarly, development and persistence of complaints of mucositis like dryness of mouth, sticky saliva, apthus ulcer, dysphagia or speech disturbance can be due to radiotherapy or drugs like cisplatin, amoxicillin, pheniremine maleate. Here, there was an overlapping between the sign and symptoms of disease progression and adverse drug reactions of chemotherapy. In the same way, causality assessment scale is unable to help us to associate causality of adverse events in the presence of confounding factor of prophylactic medications[26].

Conclusion

In conclusion, oral cavity squamous cell carcinoma is seen maximally among male farm workers, presenting at an advanced stage of disease, during the fourth or fifth decade of life, having an addiction like smoking tobacco in the form of bidi or cigarette, alcohol consumption or betel nut chewing during their lifetime.

In spite of giving various prophylactic medicines for prevention of adverse drug reactions, their incidence remains high, which affects overall treatment outcome and compliance of patients. Overall, there is a need for better anticancer agents having better efficacy with fewer side effects and also more aggressive prophylactic treatment to prevent treatment related adverse drug reactions.

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