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ORIGINAL ARTICLE

Assessment of Adverse Drug Reactions in Oral Cancer Patients Receiving Chemotherapy Treatment at Tertiary Care Centres in North-Western India

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Abstract

Background/Aim: Pharmacovigilance in oncology is imperative as antineoplastic drugs are two-edged swords whose irrational use can pose a major health problem and a needless financial burden on the patient. The aim of this study was to study the comprehensive safety profile of anti-neoplastic drugs used for treating oral cancers.
Methods: This hospital-based prospective observational study was conducted at two premiers (a government and a private) tertiary care centres in North-Western India among newly diagnosed cases of oral cancers of both sexes between the ages of 20-70 years and requiring chemotherapy treatment. The prescribing pattern of chemotherapy drugs, associated adverse effects and potential risk factors for the development of adverse effects was studied. An adverse drug reaction (ADR) causality was assessed by the WHO-UMC algorithm and preventability by Schumock and Thornton's criteria. Univariate and multivariate logistic regression analyses were used to identify the predictors related to chemotherapy-induced adverse effects.
Results: The data concerned 188 patients, of which 64.3 % developed chemotherapy-related adverse effects. Among the prescribed anti-neoplastic drugs, a combination of 5-Fluorouracil, Cisplatin and Paclitaxel regimen was associated with the majority (91.42 %) of the adverse effects. Alopecia was the most common adverse effect noted in 26.44 % of patients, followed by nausea and anaemia in 15.7 % and 9.9 % of patients, respectively. Independent predictors of chemotherapy-related adverse effects were site (Adjusted odds ratio [AOR] = 1.95; 95 % CI 1.04 - 3.62, p = 0.03), chemotherapy and radiotherapy treatment (AOR = 5.00; 95 % CI 2.62 - 9.53, p < 0.001), combination regimen of 5-Fluorouracil, Cisplatin and Paclitaxel (AOR = 8.68; 95 % CI 2.55 - 29.48, p = 0.001), associated comorbidities (AOR = 16.68; 95 % CI 2.45 - 28.34, p < 0.001). Causality assessment revealed most adverse effects (82.64 %) to be possible.
Conclusion: The adverse effect varies with the type of regimen which is prescribed for the patient. Site of cancer, concomitant radiotherapy treatment and associated comorbidities were the identifiable risk factors for developing adverse effects. Onco-pharmacovigilance studies in the future will help to provide tailored treatment to patients and improve their quality of life.

Key words: Adverse drug reactions; Causality assessment; Chemotherapy; Oral cancers; Risk factors.

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Introduction

In developing countries like India, noncommunicable diseases are the biggest cause of premature death.[1] New cancer patients are estimated to be 1.1 million per year in India,[2] while the mortali-

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ty associated with it is about 0.6 million people each year.[3] Tobacco-related cancers itself are the major culprits in the mortality associated with cancer.[3] In Jaipur City located in north-western region of India, the four leading sites of cancer in males are tobacco-related cancers – lung, tongue, mouth and oesophagus, followed by prostate cancer, as reported in the National Cancer Registry Programme of the Government of India.[4]

World Health Organization (WHO) defines adverse effects[5] as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function." The main modalities used for cancer treatment include surgery, radiation, chemotherapy or immunotherapy. Cancer chemotherapy utilises either single or combination of anti-neoplastic drugs in a standardised regimen as prescribed for the management of neoplasia.[6] It is imperative to monitor adverse drug reactions (ADRs) in oncology, where pharmacotherapy is linked by high prevalence of drug-related complications due to their narrow therapeutic window.[7] Chemotherapy adversely affects the quality of life in cancer patients and may land them in a series of misfortunes that includes feelings of low mood, restricted mobility, low sexual desire, reduced social interaction and undermining capabilities at work.[8]

Although few studies pertaining to pharmacovigilance in cancer patients have been undertaken in the past, all were generally designed as snapshot studies with relatively little attention to a particular cancer and its associated risk factors in the target populations.[9-12] Therefore, the present study was planned among the oral cancer patients with the aim of providing them with tailored pharmacotherapy with fewer adverse effects and complications.

Methods

Ethical consideration

This study was approved by the institutional ethics committee of SMS Medical College (Reference No 3206 MC/EC/2017). It was conducted according to the Declaration of Helsinki. Written informed consent was obtained from the patients prior to their recruitment.

Participants and eligibility

Inclusion criteria for the study were: a) patients between 20-70 years of age b) newly admitted and confirmed cases (by histopathology) of the squamous cell carcinoma of the oral cavity and oropharynx which required treatment with chemotherapy (irrespective of adjuvant setting, neo-adjuvant setting, with or without radiotherapy, as radical definitive chemo-radiotherapy or as palliative treatment) and in any of the stage I, II, III and IV (according to AJCC of head and neck cancers). The non-inclusion criteria for the study were pregnant and lactating females, patients of psychiatric disorders, patients suffering from HIV and hepatitis B infection.

Sample size and sampling technique

Taking prevalence (P) of ADRs as 58.6 %, confidence interval (CI) as 95 % and 5 % relative precision, the sample size was worked out to be 94 participants.[13] However, a pilot study was conducted in 100 patients for a month and the final sample size for the study was calculated as 188 to compensate for any loss to follow up. For the data collection two days of the same week of the month were chosen randomly by a computer-based random number generator to collect data from both hospitals.

This was a prospective and observational study conducted among 188 patients receiving chemotherapy treatment from May 2017 to December 2017 in two leading government and private charitable tertiary care centres in North-Western India, Swai Man Singh Medical College and Bhagwan Mahaveer Cancer Centre, Jaipur. These institution catered to the needs of patients with various haematologic and solid malignancies, with an average daily volume of more than 150 patients in the outpatient department and 50-80 patients were admitted daily in the indoor facility.

Study variables

A comprehensive review of each patient's medical record was conducted from the day of chemotherapy prescription to 90 days post-start of therapy. Parameters included age, gender, diagnosis, type of tobacco consumption, site of oral cancer, chemotherapy prescribed, dose and directions, any documented follow-ups and laboratory investigations like complete blood counts and other blood investigations to access the functioning of kidney and liver. Drug-related toxicities were identified by interviewing each patient personal-

ly for any chemotherapy-related adverse effects during oncology/haematology clinic visits and by personal telephonic encounters. A study proforma was developed in accordance with the ADR reporting form of the Central Drugs Standard Control Organisation (CDSCO), Government of India, for collecting data regarding the patients' demographic profile, the details of drugs received during chemotherapy sessions, route, dose and number of chemotherapy cycles, any pre-existing comorbidities and any adverse effects following chemotherapy cycles. The patients were monitored throughout and interviewed personally by the nursing staff and clinical pharmacist for ADR checks at three separate points of time - 30, 60 and 90 days (2 weeks at each interval) post-initiation of the chemotherapy drug. Adverse events were classified according to WHO-UMC causality assessment scale and the severity of these were assessed by Modified Hartwig and Siegel Scale.
The chemotherapy treatment (including the drug, dose, frequency and number of cycles) for each patient was decided by the consultant medical oncologist and team in accordance with the Indian Council for Medical Research guidelines and NCCN guidelines and evidence based protocols for different stages. The clinical pharmacists assisted the oncologists and nurses with treatment and therapy plans, ensuring appropriate supportive care options for each patient and addressing any drug-related questions, including ADRs. To manage the myelosuppression observed in the patients in this study, supportive intervention with haematopoietic growth factors (granulocyte colony-stimulating factors [G-CSFs] and erythropoiesis-stimulating agents [ESAs]) and blood transfusions were given.

Study outcomes

The primary outcome of interest was the incidence and pattern of chemotherapy-related ADRs occurring within 90 days of a patient starting treatment. The secondary outcomes of interest were predicting risk factors for the development of these adverse effects.

Statistical analysis

The collected data were analysed using IBM SPSS (Statistical Package for Social Sciences) statistics for Windows, version XX.0 (International Business Machines Corporation (IBM) Corp., Armonk, N.Y., USA). At first, all the prescriptions were coded using automated generated codes to avoid any information-related bias as the prescriptions were collected from two different settings that is government and private. Descriptive statistics (ie number and range) were used to analyse patients' demographic characteristics. For risk estimate analysis, the variables with p-values of < 0.2 in the binary univariate analysis were included in the multiple binary logistic regressions to control the effect of confounding variables. $P \leq 0.05$ was considered statistically significant and the results were reported as odds ratios (ORs) with 95 % confidence intervals (CIs).

Results

Demographic characteristic of study population

One hundred eighty-eight patients who received chemotherapy alone or in combination with other treatment were enrolled for this study. Out of that number 81 patients had oral cavity cancers, while 107 had cancer of oropharynx. There was a male preponderance of oral cancers (91.4 %). The majority of the patients receiving chemotherapy treatment were in the age group of 41-50 years. Both males and females were more likely to be diagnosed in stage 3 (52.65 %) as depicted in Table 1. 19.68 % of the patients suffered from different comorbidities.

Table 1: Demographics of patients

Characteristics	Patients (N = 188)
Age (years) - mean (range)	45.6 (24-68)
Male (%)	171 (91.4 %)
Tobacco history	
Yes	167
No	21
Site	
Oral cavity	81
Oropharynx	107
Stage*	
I	6
II	27
III	99
IV	56
Co-morbidities	
Hypertension	18
Diabetes	14
Rheumatoid arthritis	3
Hypothyroidism	2

**Stage according to AJCC of head and neck cancers;*

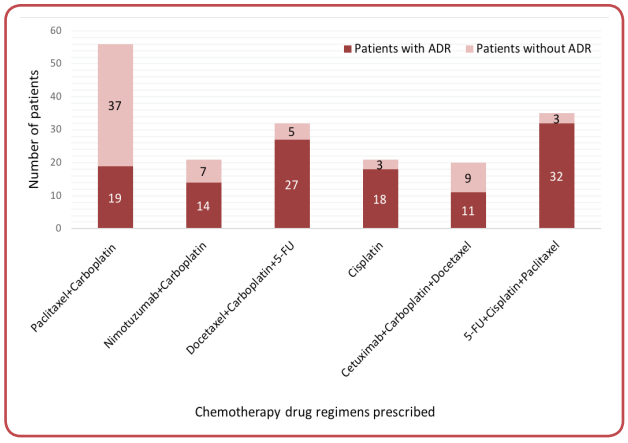

Figure 1: Prescribing pattern of chemotherapy drugs and distribution of associated adverse effects

5FU: 5- Fluorouracil;

Prescribing pattern and adverse drug reactions profile in oral cancer patients

Figure 1 shows that Paclitaxel and Carboplatin combination was the most frequently prescribed regimen for 29.8 % of the patients, while the Cetuximab, Carboplatin and Docetaxel combination was the least frequently prescribed regimen, prescribed to only 10.64 % of the patients. 64.3 % of patients developed 15 different types of ADRs, with the gastrointestinal system commonly affected (33.06 %) followed by skin (32.23 %). The 5-Fluorouracil, Cisplatin and Paclitaxel regimens were associated with majority (91.42 %) of the adverse effects. The majority (66.2 %) of the adverse effects occurred in male patients and the age group of 45-60 years was commonly implicated. Alopecia was the most common adverse effect noted in 26.44 % of patients, followed by nausea and anaemia in 15.7 % and 9.9 % of patients, respectively. 82.64 % of ADRs were classified as possible and 17.35 % as probable according to the WHO-UMC causality assessment scale as depicted in Table 2. Most reactions were mild (94.21 %) in nature and the remain were moderate (5.78 %), as assessed by Modified Hartwig and Siegel Scale. Furthermore, only 52.2 % of the drugs were prescribed by their generic names. The average number of drugs per prescription was 7.4. On an average, one anti-peptic ulcer drug was given to each patient.

Risk factors for development of adverse reactions

Risk estimates (Table 3) revealed that there was a significant association between site (adjusted odds ratio [AOR] = 1.95; 95 % CI 1.04 - 3.62, p = 0.03), chemotherapy and radiotherapy treatment (AOR = 5.00; 95 % CI 2.62 - 9.53, p < 0.001), combination regimen of 5-Fluorouracil, Cisplatin and Paclitaxel (AOR = 8.68; 95 % CI 2.55 - 29.48, p = 0.001), associated comorbidities (AOR = 16.68; 95 % CI 2.45 - 28.34, p < 0.001) and development of ADRs. However, age failed to show a statistically significant difference in risk of developing ADR.

Table 2: Pattern of adverse drug reactions (ADRs) to anticancer drugs and causality assessment of associated adverse effects (World Health Organization UMC causality assessment scale)

Regimen	ADRs	Number of patients	Causality assessment
5-Fluorouracil + Cisplatin + Paclitaxel	Alopecia	8	All Possible
	Anorexia	4	All Possible
	Dysgeusia	5	Possible: 4, Probable: 1
	Nail Discoloration	3	Possible: 2, Probable: 1
	Nausea	6	All Possible
	Anaemia	4	Possible: 3, Probable: 1
	Leukopenia	2	All Possible
	Neutropenia	2	Possible:1, Probable: 1
	Thrombocytopenia	1	All Probable
Cetuximab + Carboplatin + Docetaxel	Alopecia	2	All Possible
	Erythema (around nails)	2	All Possible
	Fever	3	Possible: 1, Probable: 2
	Mucositis	5	All Possible
Cisplatin	Alopecia	5	Possible: 4, Probable: 1
	Mucositis	4	All Possible
	Nausea	5	All Possible
	Anaemia	2	Possible: 1,Probable: 1
	Leukopenia	2	All Probable
Docetaxel + Carboplatin + 5-Fluorouracil	Alopecia	9	All Possible
	Anorexia	3	Possible: 2, Probable: 1
	Diarrhoea	2	All Possible
	Dysgeusia	1	All Possible
	Nail discoloration	1	All Probable
	Fever	3	All Possible
	Nausea	6	Possible: 5, Probable: 1
	Anaemia	2	Possible: 1, Probable: 1
Nimotuzumab + Carboplatin	Fatigue	6	All Possible
	Headache	2	Possible: 1, Probable: 1
	Nausea	2	All Possible
	Anaemia	4	All Possible
Paclitaxel + Carboplatin	Alopecia	8	Possible: 5, Probable: 3
	Anorexia	4	Possible: 3, Probable: 1
	Diarrhoea	2	Possible: 1, Probable: 1
	Erythema	1	All Possible

Table 3: Risk factors analysis of the patients experiencing adverse effects

Risk factors	AOR	Lower 95 % CI	Upper 95 % CI	p-value
Age				
Site (Oral cavity/Oropharynx)	1.95	1.04	3.62	0.03
Treatment (Chemotherapy + Radiotherapy)	5.00	2.62	9.53	< 0.001
Chemotherapy drug regimen (5-Fluorouracil + Cisplatin + Paclitaxel)	8.68	2.55	29.48	< 0.001
Comorbidity	8.33	2.45	28.34	< 0.001

AOR = Adjusted Odds Ratio; CI = Confidence Interval; p-value ≤ 0.05 was considered statistically significant;

Discussion

Identification and reporting of ADRs and associated predictors in cancer patients is crucial in developing preventive strategies and improve their quality of life. With the development of new and targeted chemotherapy drugs, there has been a new revolution in the field of onco-pharmacology, mainly based on a tailored approach to cater to the needs of specific individuals.[14] Nonetheless, clinicians can't turn a blind eye to the adverse effects antineoplastic drugs can pose. In the current study, the pattern and possible predictors of adverse effects were evaluated in 188 oral cancer patients.

Although there was a male preponderance for oral cancers in this study, which was consistent with other previous studies,[15-17] no gender difference in the development of adverse effects was found in risk estimate analysis. These findings are contradictory to a few previous studies in cancer patients, with female gender being a significant risk factor for the development of ADRs.[18, 19] The possible reason for this difference could be the inclusion criteria for this study, which is limited to oral cancer patients only, which itself is prevalent among males as compared to females. Majority of the adverse effects in the study occurred in 45–60 years age group, which can be correlated with the high age-related morbidity in this particular age group.[20]

The drug utilisation pattern in the present study revealed that the most common class of cytotoxic agents prescribed for oral cancer was Paclitaxel and Carboplatin combination. These results are also mirrored in previous studies by Murti et al.[11] Another previous study by Motghare et al reported oral Cisplatin to be the most commonly prescribed therapy for oral cancer patients, followed by 5-Fluorouracil, Paclitaxel, Carboplatin and Docetaxel.[10]

Cancer chemotherapy includes cytotoxic medicines accompanied by adjuvant and supplementary therapeutic measures to combat their adverse effects. Clinical pharmacists and nurses, being an integral part of the oncology care team, provided their counselling service to all the new patients awaiting their first-cycle of chemotherapy and also discussed in detail about the potential adverse effects and their possible treatment to the patients and their caregivers. Furthermore, they also developed educational materials for the patients and their caregivers in a local language that assisted better monitoring of the treatment and reporting of the treatment-related concerns, including the adverse reactions.

Proton pump inhibitors, H2 antagonists and steroids were frequently used prophylactically as well as therapeutically for the management of chemotherapy-induced nausea and vomiting caused by different drug regimens. Newer anti-emetics and neurokinin-1 receptor antagonists like aprepitant were not prescribed as frequently.[21] This could be the possible reason for nausea to be the major adverse effect noted in the study. While destroying cancer cells, chemotherapy drugs can also damage rapidly dividing cells of bone marrow, resulting in myelosuppression, thus affecting white blood cells, platelets and red blood cells.[22]

Some of the chemotherapy related adverse effects were self-remitting and did not require any treatment. Alopecia seen in the patients was acute and reversible and was noted after the first chemotherapy cycle itself. The lost hair gradually regrows starting three to six months after the last chemotherapy cycle, returning to baseline progressively.[23] Similarly, the nail changes noted in the patients were self-remitting and required no treatment.[23]

In presented study, the average number of other drugs per prescription was 7.4 while the average number of cytotoxic drugs per prescription was 2.3. This is contradictory to the findings of studies in Nepal and in Karnataka state in India, with an average number of 1.97 and 1.78 cytotoxic medications prescribed per prescription.[24, 25] The increased number of drugs per prescription is an indicator of polypharmacy practice, which is quite prevalent in cancer patients as well as they are provided with supportive treatment apart from chemotherapy.[26]

Despite recommendations to use generic names (rather than brand names), only 52.2 % of cytotoxic drugs were prescribed with generic names.[27] 71.4 % of the prescribed drugs were from the essential medicine list. These results signify irrational prescribing practices and the reason for this difference could be the two different study sites considered for the study. The patients were recruited from private as well as government tertiary care hospitals. In a government setting, all the drugs were prescribed from Essential Medicine List and by their generic names, but this was not the practice observed in the private setting.

Well planned pharmacovigilance studies in cancer patients ensured proper reporting of the ADRs in these patients. 64.4 % patients in this study developed various ADRs. This finding is slightly contrary to that of Murti et al, which showed adverse effects in 87.5 % of oral cancer patients in the Bihar region receiving chemotherapy drugs.[11] The most noticeable finding was that all the ADRs recorded in this study were collected by the active surveillance method. Drug safety methods can undergo a major overhaul if such active surveillance practices are initiated.

Only chemotherapy-related ADRs were taken into consideration for this study. The majority of the ADRs (91.42 %) were due to the combination regimens of 5-Fluorouracil, Paclitaxel and Cisplatin. Alopecia was the most common adverse effect noted in 26.44 % patients, followed by nausea and anaemia in 15.7 % and 9.9 % patients, respectively. These findings were quite similar to a study by Saini et al.[6] However, these results were in contrast to a few previous studies which reported neutropenia and constipation as the most common ADRs.[28, 29] This difference could be due to a difference in the usage pattern of different chemotherapy drugs used to treat different malignancies.

The WHO causality assessment scale indicated that 82.64 % of the reactions were "possible". The reason for lack of any certain category of ADRs could be the multiple drugs which are being prescribed to cancer patients under different drug regimens. Sometimes, other concomitant drugs in the regimen might contribute to the observed adverse effects. Furthermore, it cannot be completely ruled out that associated comorbidities and the cancer disease itself may sometimes mimic an ADR in these patients.

The strength of this study is that it highlights the potential risk factors like the site, nature of treatment (chemotherapy/radiotherapy), prescribed drug regimen and associated comorbidities for the development of ADRs in oral cancer patients being treated at government and private tertiary care settings. These risk factors should be taken into account while deciding the line of treatment for these patients. The study findings further emphasised the need for new policies and educational strategies that should be undertaken to promote rational and generic prescribing in cancer patients.

One limitation of this study was that only oral cancer patients from the specific geographical location in India were included to study the adverse effects and the potential risk factors, while other cancers were not taken into account, so the results are not generalisable for other types of cancers with different geographical distribution. Also the patients were followed for a short duration of time, so long term adverse effects could not be studied. It can be expected that in the near future, more studies will be undertaken among different cancer patients with a long follow-up period so that pharmacovigilance database can be setup for developing countries like India with diverse pharmaco-genetic variation.

Conclusion

The adverse effects following chemotherapy depends on the drug regimen chosen for a patient. Few identifiable risk factors for developing adverse effects based on this study were the site of cancer, concomitant radiotherapy treatment and associated comorbidities. Onco-pharmacovigilance studies, if undertaken, can play an important role in the better management of patients receiving chemotherapy treatment by early detection and timely management of drug-related toxicities. Furthermore, identification of the predictors can aid in improving the prescribing pattern in cancer patients, thereby decreasing hospitalisations and economic burden and improving their quality of life.

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Conflict of interest

None.

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