Original Article

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A Pharmacoepidemiological Safety Study in Oral Cancer Patients in Jaipur City

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ABSTRACT

Introduction: Chemotherapy for cancer patients is a mixed blessing. It is like a double edged sword, improving survival rate in the patients, assuring better quality of life but simultaneously also exposing them to various adverse drug reactions. This mandates regular and frequent pharmacovigilance studies in oncology to safeguard the patients against the adverse effects and provide timely management of complications which ensues.

Methodology: The study was undertaken to observe the pattern of suspected adverse drug reactions of cancer chemotherapy in oral cancer patients aged more than twenty years, attending two tertiary care hospitals in Jaipur city. Data were analyzed using SPSS for Windows, version 16.0 Chicago (SPSS Inc.) and presented in the form of descriptive statistics.

Results: 64.36% patients developed fifteen different types of adverse drug reactions. Alopecia was the most common adverse effects followed by nausea, anemia, and anorexia. Paclitaxel and Carboplatin regimen was safe compared to others (p=0.6). Causality assessment revealed that most of the adverse effects (82.5%) were in possible category of WHO causality assessment scale.

Conclusion: Oral cancer patients are susceptible to a variety of adverse effects. Pharmacovigilance of anti-cancer drugs needs to be researched further and use of precautionary measures needs to be intensified to decrease the incidence of adverse effects.

INTRODUCTION

Early analysis of oral cancers and well planned treatment in nick of time is a preeminent health priority as it constitutes thirty percent of all the cancers in our country.[1] Many new antineoplastic drugs are now flooding the market because of the accelerated approval they get by FDA on the basis of 'surrogate end points' as they improve quality of life in cancer patients.[2] With many new oncology drugs hitting the market, the susceptibility of the patients to variety of adverse effects like fatigue, neutropenia, nausea and vomiting, diarrhoea, mucositis-stomatitis, and hair loss also increases. Unfortunately, these adverse effects are accounted as 'normal' and do not influence the therapeutic decisions in majority of the cases.[3]

Though pharmacovigilance program of India is running smoothly since 2010[4], still under reporting of adverse drug reaction is rampant in oncology as majority of the oncologists perceive the adverse effects as inevitable.[3] It is in this regard, this study was undertaken with the aim to identify the pattern of adverse drug reactions (ADR) in patients being treated for oral cancers in Jaipur city.

METHODS

This was a prospective study undertaken among oral cavity and oropharyngeal cancer (oral cancers collectively) patients attending the two hospitals in Jaipur city from May 2017 to May 2018. These centers were chosen as they include both major government and private referral centers in Jaipur city. The research methods and investigational tools in this study were approved by both study centers. All of the respondents had given a written informed consent to participate in the study and consented to the publication of the data thereafter.

Patients between 20-70 years of age and those diagnosed histologically and clinically with oral and oropharyngeal cancers were included in the study. Those with adverse drug reactions caused due to error in administration and drug overdose, pregnant and lactating females, patients

with other comorbidities like end organ damage, *HIV*, *HPV*, and Hepatitis B infection were excluded. Suspected adverse drug reaction reporting form of Pharmacovigilance Programme of India (PvPI) was used as evaluation tool in this study. Consultant oncologist and nursing staff consulted every patient for the development of any adverse drug reaction after each chemotherapy treatment cycle. Thereafter, the suspected adverse drug reaction forms were filled for those patients who experienced ADRs and causality assessment was done with the help of coordinator of pharmacovigilance centre using WHO Causality Assessment Scale.[5] Patients were followed for another six months post treatment for occurrence of any adverse effect.

The sample size was calculated to be 400 at 5% precision and 95% confidence interval based on previous studies,[6,7] with compensation for loss to follow-up. At both the sites on two randomly chosen days of the same week of the month, the data were collected over six and half month period that is from May 2017 till mid of December 2017. If the estimated number of patients did not reach eight patients/day, an additional day was chosen randomly in the following week and if that "additional day" was falling on a previously chosen day, then to eliminate the overlap we randomly drew lots from the cluster of remaining days until overlap could be overcome. Data were analyzed using SPSS for Windows, version 16.0 Chicago (SPSS Inc.) and presented in the form of descriptive statistics. Chi square test was used for statistical analysis and p-value < 0.05 was considered statistically significant.

RESULTS

Out of the total 400 patients, only 188 patients received chemotherapy treatment. Chemotherapy was advised to 81 oral cavity cancer and 107 oropharyngeal cancer patients. There was a statistically significant difference (p=0.03) in patients experiencing adverse effects and those not experiencing adverse effects (Table 1).

Table 1: Distribution of patients according to the adverse effects (n = 188)

	Patients experienced adverse effects	Patients didn't experience adverse effects	p value*
Oral cavity cancers (N = 81, 43.0%)	59 (72.8%)	22 (27.1%)	0.007
Oropharyngeal cancers (N = 107, 56.9%)	62 (57.9%)	45 (42.0%)	0.03

*p<0.05- Significant

Table 2: Adverse drug reactions (ADRs) distribution in different organ systems

Organ system involved	ADRs	Frequency, N (%)
Haematological system (15.7%)	Anaemia	12 (9.92%)
	Leucopenia	4 (3.30%)
	Thrombocytopenia	1 (0.83%)
	Neutropenia	2 (1.65%)
Gastrointestinal system (33.06%)	Nausea	19 (15.7%)
	Anorexia	11 (9.01%)
	Diarrhoea	4 (3.3%)
	Disgusea	6 (4.96%)
Skin (32.23%)	Alopecia	32 (26.45%)
	Erythema	3 (2.48%)
	Nail discoloration	4 (3.30%)
General disorders (19.01%)	Fatigue	6 (4.96%)
	Fever	6 (4.96%)
	Headache	2 (1.65%)
	Mucositis	9 (7.44%)

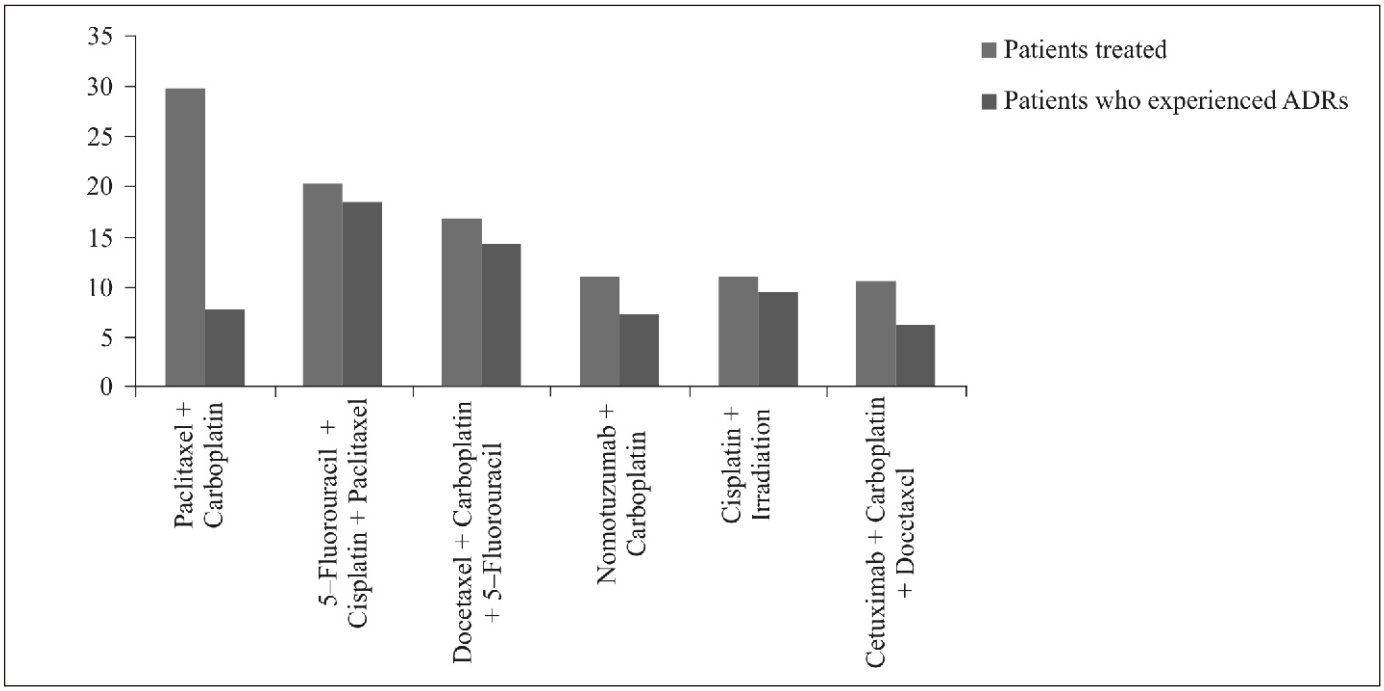

Figure 1: Adverse drug reactions (ADR) profile of different drug regimen for oral and oropharyngeal cancer patients.

Out of 188 patients, 121 patients (64.36%) developed fifteen different types of adverse drug reactions (ADRs) as depicted in Table 2. Alopecia was the most common adverse effect noted in 32 patients, followed by nausea in 19 patients and anemia and anorexia in 12 and 11 patients respectively (Table 2). Majority (66.2%) of the adverse effects occurred in male patients. Adverse effects were common in the age group of 50-60 years.

Paclitaxel and Carboplatin were the most common drug (29.8%) combination prescribed to the patients and also the safest regimen ($p = 0.6$) as shown in figure 1. After performing the causality assessment, it was found that most of the ADRs (82.5%) were in possible category of WHO causality assessment scale while 17.5% of the ADRs were in probable category. Figure 1 shows ADR profile of different drug regimen for oral and oropharyngeal cancer patients. For Paclitaxel + Carboplatin group p value was 0.6 and other regimens p value was <0.001. The p value was calculated using Chi-Square test.

DISCUSSION

National Pharmacovigilance and ADR monitoring in India and some developing countries are still in their infancies and are not yet functioning optimally.[8,9] Poor pharmacovigilance system can lead to treatment failure as the patients are not adequately safeguarded from accessing the harmful and ineffective medicines.[10] Commonly employed chemotherapy drugs used for treating oral cancers include taxanes (Paclitaxel and Docetaxel), platinum containing compounds (Cisplatin and Carboplatin), and antimetabolites (Methotrexate and 5-Fluorouracil). All these drugs possess a wide range of adverse effects due to their narrow therapeutic effects, jeopardizing quality of life in these patients.[11] Timely reporting and constant monitoring of the adverse drug reactions in cancer patients ensures their safety. This will further help to analyze the change in pattern of adverse drug effects with time and even the uncommon adverse effects can be charted out.

Though India has a population of approximately 1.24 billion, but the rate of adverse drug reaction reporting in our country is below 1%.[8] In oncology too, adverse drug reaction reporting is often overlooked because most of the oncologist believes that they are inevitable.[3,12] Other possible reasons of under reporting of adverse drug reactions in our country could be for financial incentives, fear of legal aspects, apprehension that the serious ADRs are already documented when a drug is introduced in the market, that a single report would make no difference, ignorance (that only serious ADRs are to be reported), and lack of time or work over load.[12,13]

The present study revealed that majority (66.2%) of the adverse effects occurred in male patients. Different previous studies depict a contrast in the pattern of distribution of adverse drug effects among both the gender. While in a study by Jose et al[14], majority (58.6%) of ADRs were noted in females, other studies revealed male preponderance for adverse drug reactions.[15,16]

In the present study majority of ADRs were noted in 51-60 years of age group with the mean age of 52.6 years. This is consistent with another study of Eastern India[15] while contradictory to other studies.[11,17] In our study for the treatment of oral cancers single, double, and/or triple regimen were preferred depending upon the stage and site of cancer. 121 (64.4%) patients out of total of 188 patients (who underwent chemotherapy treatment) developed ADRs in this study in contrast to the study by Murti K et al[7] in oral cancer patients in Bihar region, which showed 87.5% oral cancer patients developed adverse effects to chemotherapy drugs. Another Indian study depicting the pattern of adverse drug reactions to anticancer drugs in Bihar region, reported that all the patients receiving chemotherapy had ADRs.[18]

Despite of pre-medication with parenteral steroids, antiemetics, and other classes of drugs, the adverse effects were only reduced but not eliminated completely. Regardless the use of 5-HT_3 antagonist like Ondansetron and Granisetron, nausea and vomiting incidence could not be prevented completely, although decreased in frequency. The most frequent adverse effects noted were alopecia, nausea, anemia followed by anorexia. Alopecia started after a week of the first chemotherapy cycle and continued till the complete therapy. Cisplatin with irradiation was found to be the most common agent implicated in ADRs similar to previous studies [6,16,17] followed by Docetaxel, Carboplatin, and 5- Fluorouracil combined regimen. The treatment drugs were not withheld in any patients because of the adverse effects indicating less severe nature of adverse effect.

In the present study, World Health Organization UMC causality scale showed that 82.5% were in possible category while 17.5% of the ADRs were in probable category, in contrast to the study of Murti K[7] et al which revealed 82% of adverse drug reactions in oral cancer patients were "certain", 15% were "probable" and 3% were in "possible" category. There is paucity of data on spontaneous reporting of adverse effects of anticancer drugs despite their high potential for drug toxicity. Until adverse effects monitoring is not done for various cancers, spectrum of adverse effects of chemotherapy drugs could not be analyzed and smooth functioning of pharmacovigilance program will be at stake. Our study had few limitations. Firstly, all the observations were based mostly on patient complaints and few suitable laboratory investigations. Invasive blood monitoring for confirmation of adverse effects were not done. Therefore, biochemical/investigational ADRs like liver function test could not be determined.

CONCLUSION

Oral cancer patients receiving chemotherapy are prone to adverse effects which need to be addressed by more rigorous measures. Considering variations in genetic makeup of Indian population, pharmacovigilance in oncology will help in developing an Indian database pertaining to side effects of anticancer drugs to help the policy makers.

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