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Study of prescription patterns and adverse drug reaction monitoring in patients of oral cavity malignancies attending radiotherapy department in a tertiary care teaching institute

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Abstract

Objectives: To study prescriptions of patients having oral cavity malignancy on antineoplastic drugs and study adverse drug reaction occurred.

Methods: an observational study was carried out in radiotherapy out-patient department in tertiary care teaching institute, Nagpur after approval from Institutional Ethics Committee for 2 months period. In this prospective study, diagnosed cases of oral cavity malignancies were included. Epidemiological data and details of prescribed drugs were recorded. Collected data was analyzed for prescription pattern of antineoplastic drugs and reported adverse drug reactions.

Results: Out of 34 enrolled patients, majority were male (73.05%) with mean age 48 ± 13.29. Carcinoma of buccal mucosa (35.2%) was most common. Chemotherapy drugs commonly used were Cisplatin (79.4%), 5-fluorouracil (47%), Paclitaxel (41.1%), Carboplatin (20.5%), Docetaxel (20.5%). Monotherapy (Cisplatin) developed 4.6% ADRs, two drug therapy (Cisplatin+Paclitaxel, Cisplatin+5-fluorouracil, Carboplatin+Paclitaxel) developed 79% ADRs and three drug therapy (Cisplatin+Paclitaxel+5-fluorouracil, Cisplatin+Docetaxel+5-fluorouracil) developed 16.2% ADRs.

A total of 43 adverse reactions were reported during this study. Reactions observed were nausea (18.6%), vomiting (18.6%), anorexia (16.2%), alopecia (13.9%), diarrhea (2.3%), constipation (4.6%), weakness (18.6%), insomnia (2.3%), hemoptysis (2.3%) and black nails (2.3%). In Naranjo causality assessment, 62.7% of ADRs were probable and 37.2% were possible. In Hartwig and Siegel scale analysis, most reactions (76.7%) were of "mild" severity, 20.9% of reactions were of "moderate" severity, while 2.3% of reactions were of "severe" severity. Modified Schumock and Thornton criteria indicated that 44% of ADRs as "definitely preventable" and 55.8% of ADRs as "not preventable".

Conclusion: Study concludes that antineoplastic drugs, Cisplatin, Carboplatin, Docetaxel, Paclitaxel and 5-fluorouracil were commonly prescribed. Higher incidence of ADRs was observed with two drug therapy as compared to single drug regimen.

Keywords: Oral malignancy, Antineoplastic drug, Adverse drug reaction (ADR)

Introduction

Oral malignancy accounts for one of the commonest malignancy in the world. It is a major problem in India, for the year 2012 with estimated incidence of 10.1 cases per 100,000 population for males and 4.3 per 100,000 population in females. Estimated mortality is about 6.7 per 100,000 in males and 3.0 per 100,000 in females.[(1)]

Chemotherapy remains one of the integral components in the management of oral malignancies. They are either used alone or in combination with other modalities of management such as radiotherapy and surgery.[(2)] Patients are often treated with combination chemotherapy to minimize the chance of developing resistance. The chemotherapy drugs most often used for malignancies of oral cavity are Cisplatin, Carboplatin, 5-Fluorouracil (5-FU), Paclitaxel and Docetaxel etc. Other drugs that are used less often include Methotrexate, Ifosfamide, Bleomycin etc.[(3)]

World Health Organization (WHO) defines an ADR as "any response to a drug which is harmful, inadvertent and occurs at doses used in man for prophylaxis, diagnosis or therapy".[(4)] ADRs have been shown to be one of the top ten causes of death in US yearly[(5)] and represents a major clinical problem for humans and healthcare cost.[(6)] Chemotherapeutic drugs have a high toxicity profile and early recognition of drug toxicity helps to amend the course of drug therapy to diminish toxic effects.[(7)] Various studies had reported antineoplastic agents as common drugs class causing the ADRs.[(8)] Most of the adverse drug reaction due to antineoplastic drugs are because of extension of their therapeutic action of drugs that are distributing in all fast dividing cells.[(9)] The ADRs due to antineoplastic drugs depend on the type and dose of drugs given and duration they are taken. These ADRs can include alopecia, oral ulceration, anorexia, nausea and vomiting, diarrhea, Low blood counts etc.

The Adverse drug reaction reporting to the pharmacovigilance center from the cancer wards is less commonly found. The reason for this can be either underreporting of ADRs or effective use of preventive measures in patients receiving cancer chemotherapy. So there is felt need to report and analyze the pattern of ADRs due to antineoplastic drugs.

Drug utilization studies (DUS) are powerful exploratory studies to ascertain the role of drugs in society. Monitoring of prescriptions and DUS could identify the associated problems and provide feedback to

prescribers.[10] There is limited data available regarding the pattern of drug utilization in oral malignancies as well as ADRs to antineoplastic drugs.

Hence the present study was carried out to generate data regarding prescribed drugs use in oral cavity malignancy and to prospectively report and analyze ADRs pattern due to chemotherapeutic drugs.

Aims and Objectives

1. To study the prescriptions of patients suffering from oral cavity malignancies.
2. To detect and report ADRs in patients of oral cavity malignancies.
3. To analyze causality, severity and preventability of ADRs in patients of oral cavity malignancies.

Material and Methods

An observational study was carried out in patients suffering from oral malignancy attending OPD (Outpatient department) of radiotherapy in government medical college and hospital, Nagpur after taking institutional ethics committee approval. This was a prospective study performed for a duration of 2 months after obtaining written informed consent from patients. Demographic data, clinical findings and prescription data was collected in proforma specially designed for the study and these data was analyzed.

Prescriptions were analyzed for different category of drugs, No. of cycles, time interval between two cycles, No. of drugs from National Essential Medicine List 2015, Generic/brand name. The cancer chemotherapy to the patients was prescribed by the treating physician. There was no interference regarding treatment decisions on drugs, schedule or duration.

Patients in the study were given pre-medication as intravenous ranitidine, dexamethasone and ondansetron to avoid emesis, as the chemotherapeutic drugs have emetogenic potential. The investigator performed direct interview of the patients to obtain data regarding adverse drug reactions. Any ADR observed by investigator or treating physician were noted in details in ADR reporting form. The collected information was documented. The causality, preventability and severity of adverse drug reaction was analyzed from obtained data. Naranjo's causality assessment scale was used to determine causality of adverse drug reactions,[11] modified Schumock and Thornton scale was used to determine the Preventability of ADRs[12] and modified Hartwig and Siegel scale was used to determine the severity of ADRs.[13]

Naranjo's algorithm is a questionnaire designed by Naranjo et al and it consists of objective questions with three types of responses - yes, no or do not know. Scores for each questions are given accordingly and depending on total score the drug reaction can be classified as definite, possible or probable. In modified Schumock and Thornton scale, there are set of questions at several levels. Depending on answer of these question levels, ADRs are classified as not preventable, probably preventable and definitely preventable. In modified Hartwig and Siegel scale depending on various factors like requirement for change in treatment, duration of hospital stay, and the disability produced by the adverse drug reaction, severity of ADRs is classified as mild, moderate or severe.

Results

Out of 34 enrolled patients, majority were predominantly male (73.05%) with mean age (years) 48±13.29. Carcinoma of buccal mucosa (35.2%) was most commonly reported followed by tongue (26.4%), alveolus (23.5%), soft palate (8.8%) and hard palate (5.8%). Out of 34 prescriptions analyzed, Cisplatin was commonly prescribed antineoplastic agent (79.4%) followed by 5-fluorouracil (47%), Paclitaxel (41.1%), Carboplatin (20.5%), Docetaxel (20.5%).[Fig. 1] whereas most commonly prescribed combination therapy was cisplatin+5-fluorouracil. These chemotherapy drugs belong to different category such as pyrimidine analogs, taxanes and platinum complexes. All drugs used were from National essential list of medicines 2015, it was found that all chemotherapy drugs were prescribed by their generic names, all chemotherapeutic drugs were given by parenteral IV infusion. Patients received most commonly 1-3 cycles of chemotherapy. There was 1 week interval between two cycles [Table 1]

Table 1: Analysis of Prescriptions of patients suffering from oral malignancy.(N=34)

No. of prescriptions analysed	34
Average No. of Cycles of chemotherapy	1-3
Time interval between two cycles	1 week
% of Drugs from National Essential Medicine List	100 %
% of Drugs used by Generic Name	100%

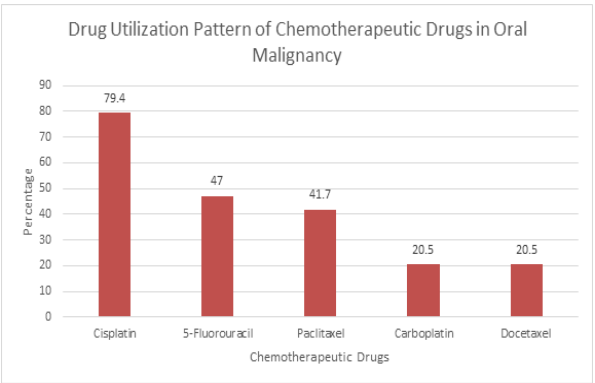

Fig. 1: Drug Utilization Pattern of Chemotherapeutic Drugs in Oral Malignancy

During this study, a total of 43 adverse reactions were reported. Various adverse drug reactions observed were nausea (18.6%), vomiting (18.6%), anorexia

(16.2%), alopecia (13.9%), diarrhea (2.3%), constipation (4.6%), weakness (18.6%), insomnia (2.3%), hemoptysis (2.3%) and black nails (2.3%). [Fig. 2]

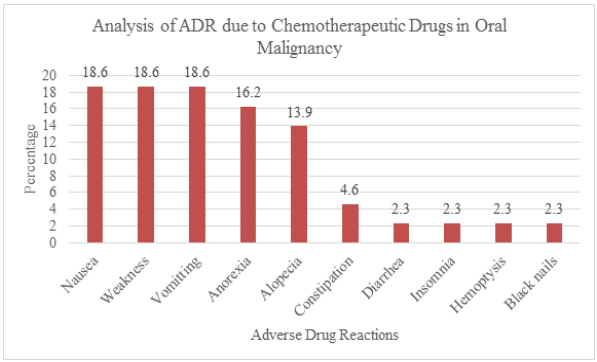

Fig. 2: Analysis of ADR due to Chemotherapeutic Drugs in Oral Malignancy

Monotherapy (cisplatin) developed 4.6% ADRs, two drug therapy (cisplatin+paclitaxel, cisplatin+5-fluorouracil, carboplatin+paclitaxel) developed 79% ADRs and three drug therapy (cisplatin+paclitaxel+5-fluorouracil, cisplatin+docetaxel+5-fluorouracil) developed 16.2% ADRs.

In Naranjo causality assessment, 62.7% of ADRs were probable (Naranjo causality assessment score 5 to 8) and 37.2% were possible (Naranjo causality assessment score 1 to 4).

In Hartwig and Siegel scale analysis, most reactions (76.7%) were of "mild" severity, 20.9% of reactions were of "moderate" severity, while 2.3% of reactions were of "severe" severity.

Modified Schumock and Thornton criteria indicated that 44% of ADRs as "definitely preventable" and 55.8% of ADRs as "not preventable".

Discussion

In present study, prescription pattern and occurrence of adverse drug reaction (ADR) were analyzed in oral malignancy patients which is highly prevalent in our country.

Gender distribution and mean age of patients in our study was similar to that reported in earlier studies.[14]

Present study reported, most commonly prescribed drugs for oral malignancy was cisplatin followed by 5-fluorouracil, paclitaxel, carboplatin, docetaxel. In previous study also Cisplatin was most commonly used anti-neoplastic agent.[15] In present study it was found that combination therapy of cisplatin+5-fluorouracil was commonly prescribed. These finding are similar to most of earlier studies[16] where cisplatin based combination therapy was most commonly prescribed drugs.

In present study, platinum compound based combination therapy developed more ADRs as compared to monotherapy which is supported by previous study conducted by Dhruw et al. In this study only prescribed medicines were considered. But it is well known that over the counter use of medicines is common in this country. And this further increases chance of drug interaction and ADRs.

In present study, the most frequent adverse drug reactions were nausea, vomiting, anorexia, and alopecia which are also found in the study conducted by Jire AS et al.[17] In present study, cisplatin was the drug causing adverse drug reaction in most of the patients. The study conducted by Laura astolfi et al. shows that there is Correlation of adverse effects and cisplatin administration in patients.[18] Nausea, vomiting, renal toxicity, ototoxicity, peripheral neuropathy, hypersensitivity reactions and electrolyte disturbances are some of the known ADRs of this drug.[19,20-26] Adequate pre-medication with parenteral ranitidine, ondansetron and dexamethasone were given to each patient. In spite of giving these medications, the frequency of nausea and vomiting was high due to antineoplastic drugs. This is because of high emetogenic potential of cisplatin.[19] The antineoplastic drugs may induce vomiting by both a central action on the chemoreceptor trigger zone (CTZ) and a peripheral action on the gastrointestinal tract. Serotonin type 3 (5-HT3) and dopamine type 2 (D2) receptors are located in the floor of the fourth ventricle in CTZ.[27] As serotonin receptors in the brain are responsible for the mechanism of acute onset vomiting, there is definite role of ondansetron in prevention of vomiting.[28] The study emphasize that there is need to improve the management of nausea and vomiting, since there was poor rate of prevention of these expected adverse effects of cisplatin.

In present study one patient reported blackening of nails as adverse drug reaction which was also found in study conducted by Ashmita et. al.[29] Some of the rarer reactions found in our study included diarrhea, constipation, weakness, insomnia, hemoptysis and black nails.

In present study, most of the ADRs had been identified as probable by Naranjo's algorithm supported by Surendiran et al.[30] In present study patients were not subjected to re challenge of the drug. This can be reason for no "definite" drug reactions found in the study. As the investigator was trained in methods of pharmacovigilance so complaints such as "unlikely" drug reactions were avoided.

Majority of adverse drug reactions were preventable. As Common ADRs like nausea and vomiting can be effectively controlled, the treating physician should anticipate and counsel the patient adequately prior to starting of therapy**.** Chemotherapy related nausea and vomiting remains a problem in many patients despite the use of 5-HT3 receptor antagonists and dexamethasone. According to study by D.G. Warr[28] use of NK 1 receptor antagonist aprepitant as add on may reduce the likelihood of vomiting and retching associated with use of chemotherapeutic agents. So modification in the management of nausea and vomiting is needed. In present study, most of the adverse drug

reactions were of mild severity and so it was not necessary to change regimen or withhold the drug for mild adverse effects.

There were several limitation in the study. First, the sample size may not be adequate to reflect the exact picture of prescribing patterns in general and in oral malignancy particular. Another shortcoming of the study is point prevalence nature of prescription related data. We cannot assume that prescription characteristics of particular medication for a given patient remains same over course of follow up of these patients. In spite of these limitations study provides overview of problems associated with use of chemotherapeutic drugs in oral malignancy patients.

Finally to conclude, present study identifies that Cisplatin was the most commonly used chemotherapeutic agent for oral malignancy and nausea was the most common ADR which is of "mild" and "level 1" severity. Thus present study emphasizes the need to improve management of ADR and pharmacovigilance program should be promoted which is highly effective in increasing the reporting of ADRs as well as help to identify infrequent adverse drug reaction caused by drugs, which will be beneficial for better outcome of oral malignancy treatment in future.

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