Original Article

Pattern of adverse drug reactions of anticancer drugs used in patients with oral cancer

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Abstract

Aim: Adverse Drug Reactions are a global problem. The incidence of oral cancer is 2% worldwide. In India, the higher incidence (30% of all cancers) of oral cancer is due to tobacco, betal chewing and alcohol. Cancer chemotherapy is more helpful in advanced stages of oral cancer. But, these drugs themselves can cause adverse drug reactions affecting the patients' health. **Objective:** To study the pattern of adverse drug reactions of anticancer drugs used in patients with oral cancer in a tertiary care hospital. **Materials and Methods:** This study was conducted in Stanley Medical College Hospital, Chennai-01 from August'2014 to February'2015 among 60 oral cancer patients receiving anticancer drugs in Dept of Oncology. This was a hospital based, prospective, observational study. ADRs were documented in suspected ADR reporting forms designed by CDSCO; causality assessment was done using Naranjo's algorithm and severity assessment by Modified Hartwig Siegel Scale. **Result:** Cisplatin, 5-Fluorouracil, Paclitaxel, Gemcitabine were the common anticancer drugs used in various combinations. The most common combinations used are 5FU + Cisplatin, Gemcitabine + Cisplatin, 5FU+ Paclitaxel+Carboplatin. ADRs were reported among 54 patients taking treatment. Causality assessment – Probable 5.6% ,Possible 94.4% ; Severity assessment – Mild 94.4%,Moderate 5.6%. **Conclusion:** The anticancer drug combinations used in the treatment of oral cancer were associated with varied adverse effects. But, the early detection of drug toxicity may be helpful in modifying the doses to minimize the toxic effects.
Keywords: ADRs, CDSCO, Cisplatin, Tertiary care hospital.

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INTRODUCTION

An Adverse drug reaction (ADR) is defined by WHO as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function"[1] Adverse drug reactions are a global problem which burdens the society. Sometimes the ADRs are so serious and severe that, the cost needed to control the morbidity and mortality is more than the cost to treat the actual disease[2]. The National Pharmacovigilance Program in India was started with the objectives of monitoring the safety of drugs and creation of an ADR database for the Indian population[3] The incidence of oral cancer is 2% worldwide. In India, the higher incidence of oral cancer is due to tobacco, betal chewing, alcohol consumption, poor oro-dental hygiene, poor nutrition and Human papilloma virus infections. Carcinomas of the oral cavity present as nonhealing ulcers, changes in the fit of dentures, or painful lesions[4]. Locally or regionally advanced disease is the stage of presentation for >50% of patients. Such patients are treated with curative intent, but not with surgery or radiotherapy alone. Combined modality therapy including surgery, radiotherapy, and chemotherapy is most successful. It can be administered as induction chemotherapy or as concomitant chemotherapy and radiation therapy. The latter is currently most commonly used and best evidence–supported. In patients with intermediate stage (stage III and early stage IV) concomitant chemo radiotherapy is given postoperatively[4]. The most common combinations used in

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our hospital are 5 FU+Cisplatin, Gemcitabine +Cisplatin, 5FU +Carboplatin + Paclitaxel. Cancer chemotherapy is more helpful in advanced stages, as the oral mucosa is particularly susceptible to cytotoxic drugs because of high epithelial turnover[5]. These drugs themselves can cause adverse drug reactions which shall affect the patients' health. Many of the adverse effects of anticancer drugs are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells.

OBJECTIVE

To study the pattern of ADR of anticancer drugs in patients with oral cancer in a tertiary care hospital.

MATERIALS AND METHODS

Study Centre: Department of Oncology, Stanley Medical College Hospital, Chennai-01.
Study Design: Prospective, observational study.
Study Duration: August'2014 to February'2015
Study Population: Oral cancer patients in Oncology department.
Sample size: 60 patients with oral cancer receiving chemotherapy.

Inclusion Criteria

1. Age 25-70 years
2. Both genders.
3. Patients in TNM stages III and IV [(4)] under cancer chemotherapy.
4. Patients receiving multiple combinations of anticancer drugs as adjuvant or neoadjuvant or palliative chemotherapy.

Exclusion Criteria

1. Age <25 and>70 years.
2. Patients with past H/O gastrointestinal or haematological disorders.
3. Patients with past H/O renal disease or liver disease.
4. Patients with past H/O CVS or CNS diseases.

Study Procedure

This study was conducted in Department of Oncology, Stanley Medical College Hospital, Chennai-01 after obtaining approval from the Institutional Ethics Committee. This was a hospital based, prospective, observational study from August'2014 to February'2015 among 60 oral cancer patients receiving anticancer drugs. The following parameters were recorded.

- Age
- Gender
- Diagnosis
- Anti cancer drugs prescribed
- Adverse drug reaction pattern
- Incidence
- Severity

Based on the age, sex, chemotherapy and symptoms given by the patients, the statistical analysis was done and results were obtained. ADRs documented in suspected ADR reporting forms designed by CDSCO and causality assessment done using Naranjo's Algorithm [(6)] and severity by Modified Hartwig Siegel scale[7]

RESULTS

The ADR reports were obtained by regular questioning of patients by the investigator in the evening hours of working days and also advised to report themselves, if there is any adverse event. The datas were entered into Excel spread sheets and descriptive statistics was used to analyze the data at the end of the study. 60 patients were observed for ADR, 54 patients had ADR. The following anticancer drugs were used for oral cancer in Dept of Oncology, Stanley Medical College Hospital, Chennai-01.

- **Group I:** Inj.5FU 500mg/m^2 IV infusion weekly for 6-8 weeks + Inj. Cisplatin 50-100 mg/m^2 slow IV infusion every 3-4 weeks.
- **Group II:** Inj.Gemcitabine 1 g/m^2 IV weekly for 7 weeks + Inj. Cisplatin 50-100 mg/m^2 slow IV infusion every 3-4 weeks.
- **Group III**: Inj.5FU 500mg/m^2 IV infusion weekly for 6-8 weeks +Inj.Paclitaxel 150mg/m^2 IV infusion every 3 weeks +Inj.Carboplatin 400 mg/m^2 IV infusion every 4 weeks.

Table 1: Age and Sex Distribution of Oral Cancer patients

Sr. No	AGE (Yrs)	Number of Patients			%
		Male	Female	Total	
1.	≤ 30	0	0	0	0
2.	31-40	11	7	18	30%
3.	41-50	14	10	24	40%
4.	51-60	5	6	11	18.3%
5.	61-70	3	4	7	11.7%

More Patients were in the age group 41-50 years. Male (55%) preponderance was seen among oral cancer patients.

Table 2: Pattern of ADRs of Anticancer drugs in oral cancer patients

Adverse Effects	DRUG COMBINATION (no of patients)			TOTAL No of PATIENTS (n= 60)	% OF PATIENTS
	I (n=24)	II (n=19)	III (n=17)		
Nausea/Vomiting	19	16	12	47	78.3%
Mucositis	15	7	11	33	55%
Anaemia	14	8	12	34	56.7%
Thrombocytopenia	4	2	5	11	18.3%
Tinglingand Numbness in limbs	4	3	6	13	21.7%
Alopecia	7	4	11	22	36.7%
Diarrhoea	2	2	3	7	11.7%
Elevated AST/ALT	2	1	2	5	8.3 %
Allergic reactions	5	4	7	16	26.7%
Arthralgia	1	1	3	5	8.3%
Skin Pigmentation	3	1	5	9	15.0%
Increased S.Creatinine level	4	3	7	14	23.3%

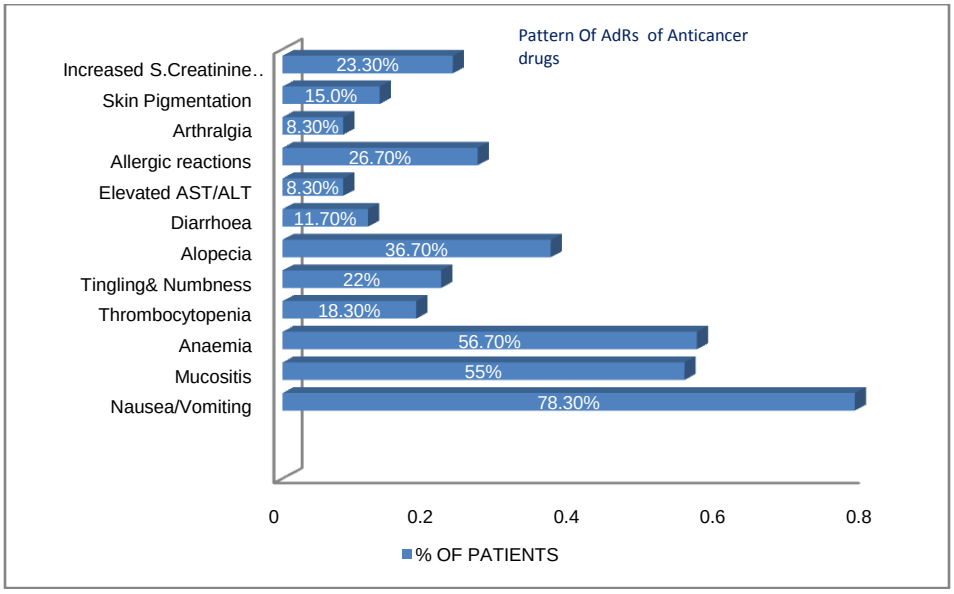

Figure 1: Pattern of ADRs of Anti Cancer Drugs in oral cancer patients

Table 2 and Figure 1 show the distribution of adverse drug reactions of anti cancer drugs in patients with oral cancer. Out of 60 patients receiving 3 different combinations of anticancer drugs, the adverse effects reported in % were as follows: nausea/vomiting (78.3%), mucositis (55%), anaemia (56.7%), thrombocytopenia (18.3%),tingling and numbness in limbs (21.7%), alopecia (36.7%), diarrhoea (11.7%), elevated AST/ALT (8.3%), allergic reactions (26.7%), arthralgia (8.3%),Skin pigmentation (15.0%), increased S.Creatinine (23.3%). Most common adverse effect observed was nausea/vomiting. Next to it were mucositis, anaemia, alopecia, thrombocytopenia, tingling and numbness, allergic reactions, increased S. Creatinine level.

Table 3: Causality assessment of adverse drug reactions

Assessment Category	No of Patients	% of Patients
Certain	0	0
Probable	3	5.6%
Possible	51	94.4%
Total	**54**	**100%**

As per Naranjo's Algorithm[6], Causality assessment was found to be probable (Score 5-8) for 5.6% cases and possible (Score 1-4) for 94.4% cases.

Table 4: Severity assessment of adverse drug reactions

Assessment Category	No of Patients	% of Patients
Mild	51	94.4%
Moderate	3	5.6%
Severe	0	0
Total	**54**	**100%**

As per Modified Hartwig Siegel Scale[7], severity assessment was found to be less severe categorized as Mild in 94.4% cases and Moderate severity in 5.6% cases.

DISCUSSION

Adverse Drug Reactions are a global problem. Cancer chemotherapy is more helpful in advanced stages of oral cancer. But, these drugs themselves can cause adverse drug reactions affecting the patients' health. Cisplatin, Carboplatin, Paclitaxel, Gemcitabine and 5-FU accounted for majority of the ADRs. This is probably due to the effect of alkylating agents and platinum analogs that interfere with DNA synthesis and function. Among 60 oral cancer patients, 33 were male and 27 were female. 54 patients (29 male and 25 female) developed ADRs within one month after receiving anti cancer drugs. According to Causality assessment, 3 ADRs were classified as Probable and 51 ADRs as Possible. The prevalence of ADRs mostly occurred in age group 41-50 years and in female patients. Severity assessment – 3 ADRs considered as Moderate and 51ADRs were found to be Mild. Nausea and vomiting are very common side effects of cancer chemotherapeutic drugs [(8)]. It was found to be 78.3%.These drugs induce vomiting by both central action on the CTZ and peripheral action on the GIT. The dominant receptors in the CTZ are 5-HT_3 and D_2. As 5HT receptors in the brain are involved in the mechanism of acute onset vomiting, ondansetron helps in its prevention. Pre-treatment values of complete hemogram were taken for every patient before each cycle and post treatment assessment was done only if clinically indicated. There were reports of anaemia and thrombocytopenia in 56.7% and 18.3% patients respectively. Although usually not life threatening, anaemia is the most common haematological complication of chemotherapy[9]. Antimetabolites like 5-FU and Capecitabine mainly acts by inhibiting thymidylate synthase which causes alteration in RNA processing and inhibits DNA synthesis and function. This may be the reason for more ADRs on bone marrow and buccal mucosa. This finding is consistent with the study conducted by Poddar *et al*, where antimetabolites and alkylating agents were related with 80% of ADRs. Diarrhoea, Mucositis occurs mainly due to decrease in the rate of renewal of GI mucosal lining. These ADRs are more related with 5 FU[10], MTX, mTOR inhibitors. The most effective means of preventing mucositis is through good oral hygiene[11-15.] Alopecia occurs due to damage to the cells in hair follicles. Drugs like MTX, Paclitaxel, Ifosphamide produces partial or complete alopecia. Skin pigmentation, photosensitivity may be due to 5FU, MTX, Capecitabine[11]. Peripheral neuropathy is a dose limiting toxicity of platinum compounds, also seen with Paclitaxel, Capecitabine and oxaliplatin.[12] Nephrotoxicity is seen more with platinum compounds, because they are extensively cleared by kidneys and excreted in urine[13]. Allergic reactions appear to be more common with Carboplatin, Cisplatin, Paclitaxel and Etoposide[12, 14]. Arthralgia is seen more in patients receiving Paclitaxel, Docetaxel, and 5FU [5].

Most of the adverse drug reactions were not preventable because of their poor predictability and poorly understood causative mechanisms. Common ADRs like nausea and vomiting can be effectively controlled by adequate pre-medication. Hence, the physician should anticipate and counsel the patient adequately prior to the chemotherapy. Most of the ADRs were less severe. So, there was no need to change or withhold the drug for milder adverse effects.

CONCLUSION

Anticancer drugs have a narrow therapeutic index. Many of the adverse effects of anticancer drugs are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells. Most of the adverse drug reactions in this study were mild, but not preventable; hence they do not affect the treatment. Early detection of the drug toxicity helps to modify the dose or drug regimen to minimize the toxicities. This study also emphasizes the need to improve pharmacovigilance awareness among physicians in order to improve the pharmacovigilance system in India.

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