Original Article

Patterns of Adverse Drug Reactions Experienced by Head and Neck Cancer (HNC) Patients On Chemotherapy with or Without Concurrent Radiotherapy in A Tertiary Care Center: A Cross- Sectional Study

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Abstract

Background: The aim of this study was to assess the patterns, frequency, causality and severity of ADRs associated with chemotherapy alone or with concurrent chemoradiotherapy. **Materials and Methods:** All the patients diagnosed with HNC and on treatment with chemotherapy or concurrent chemo-radiotherapy were included in the study. The type of chemotherapy drugs, presence or absence of radiotherapy, suspected ADR occurrence and category of ADR was noted. The causality of ADRs was evaluated using WHO-UMC Causality Assessment Scale and Naranjo's causality assessment algorithm while severity was assessed using Modified Hartwig and Siegal Scale. **Results:** 323 patients who met the inclusion criteria were enrolled. Five types of chemotherapeutic drugs were administered to the patients depending on the cancer type. Cisplatin (79.2%) was the most common drug prescribed as a single agent with radiotherapy. The number of ADR was more in CTRT (n=259) group as compared to chemotherapy group (n=42). 975 ADRs of 14 types were observed among which nausea and vomiting was most common ADR seen in 172 patients, followed by fatigue in 128 patients. The difference in frequency of ADR was statistically significant (p value<0.001) between CTRT group compared to radiotherapy and chemotherapy group except for nausea and vomiting, mucositis, myelosuppresion and nephrotoxicity. Most of the ADRs were mild (63.5). Severity of ADR between the CTRT, CT and RT groups was statistically significant (p value<0.01). Most of the ADRs were categorized as possible after the causality assessment. **Conclusion:** Use of concurrent chemoradiotherapy though beneficial, caused more ADRs than chemotherapy alone or radiotherapy alone.

Keywords: Head and neck Cancer, Concurrent chemoradiotherapy, adverse drug reactions, Causality assessment, severity.

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Introduction

Head and neck cancer (HNC) is ranked seventh most prevalent cancer worldwide and third most common cancer according to the Global Cancer Statistics of 2022.[1] In India, HNC constitutes 30% of all the cancers. The Age-standardised incidence rate of HNC was 25.9 and 8.0 per 100000 populations respectively in males and females.[2] The GLOBOCAN 2022 database includes seven types of head and neck cancers, including the lip and oral cavity, hypopharynx, nasopharynx, oropharynx, salivary gland, larynx, and thyroid cancer. The age-standardized rate (ASR) and crude rate of incidence were highest for the lip and oral cavity cancers (9.91 and 10.22 respectively).[3] Treatment plan for various cancers include surgery, chemotherapy, radiotherapy, immunotherapy and monoclonal antibody therapy. The preference of treatment plan depends on the location and grade of tumor, stage of the disease, general state of the patient and the cost of the treatment.[4] Chemotherapy like cisplatin, carboplatin, paclitaxel, gemcitabine, docetaxel, 5-flurouracil either alone or in combination is used.[5]

Adverse drug reactions (ADRs) are common among cancer patients undergoing cancer chemotherapy or radiotherapy and also the leading causes of morbidity, mortality or decrease survival rates. Further, the ADRs of anticancer drugs are intensified by using combination of drugs compared to a single-drug therapy or using concurrent chemoradiotherapy compared with chemotherapy alone or radiotherapy alone.[6,7,8] The ADRs are unavoidable but careful monitoring can lead to timely management of the ADRs.[9]

Studies addressing ADRs associated with chemotherapy, radiotherapy and concurrent chemoradiotherapy become beneficial to modulate the drug dosages or schedules and help in minimizing the ADRs. There is paucity in data related to ADRs associated with concurrent chemoradiotherapy. Hence, this study was conducted to assess the patterns, frequency, causality and severity of ADRs associated with chemotherapy alone or with concurrent chemoradiotherapy.

Materials and Methods

The present study was a prospective, observational study conducted in a tertiary care hospital in the Department of

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Pharmacology in collaboration with Department of Radiation Oncology for 4months (FEB 2025 to MAY 2025). The study was started after obtaining approval from Institutional Ethics Committee (IEC/RMCH/05/2025/JAN). At first, 350 patients were included in the study after obtaining informed consent from the patients, but only 323 patients were enrolled finally. The remaining 27 patients were neglected because of insufficient data. All the patients diagnosed with HNC and on treatment with chemotherapy or concurrent chemo- radiotherapy were included in the study. Pregnant and lactating women, patients who were not willing to participate in the study and who were unable to respond were excluded in this study. A separate data entry form was prepared to record patient demographic details, type of cancer affected, type of chemotherapy drugs, presence or absence of radiotherapy, suspected ADR occurrence and category and outcome of ADR. The causality of ADRs were evaluated using WHO-UMC Causality Assessment Scale,[10] and Naranjo's causality assessment algorithm,[11] while severity was assessed using Modified Hartwig and Siegal Scale.[12] All the required details of the suspected ADRs were collected and documented in Suspected Adverse Drug Reaction Reporting Form (version 1.3) provided by CDSCO website.

Sample size: Using Prevalence rate, the following formula is used to determine appropriate sample size, $n = \frac{z2*(PR*(1-PR)}{d^2}$ where, Incidence Rate is 0.3 (Bagal S et al),[2] Z-score is 1.96 and Margin of Error (d) is 0.05. Therefore, sample size is 323.

Statistical Analysis: The pattern of ADRs thus obtained was analysed using Jamovi software version 2.6.26 and MS excel. At the time of data analysis, Pearson's test was used to determine level of significance and Probability value <0.05 was considered as significant. Graphs and tables were drawn with the help of Jamovi software.

Results

323 patients who met the inclusion criteria were enrolled in the study. Out of the total patients, 86.37% were males. The patients were receiving either chemotherapy (CT), radiotherapy (RT) or both the therapy (CTRT). Mean age of the patients receiving CTRT was 46.9±10.3 years, chemotherapy group was 47.6 ± 13.1 years and radiotherapy group was 47.7± 6.80 years. The ADRs was more in patients in the age group 41-50 years (36.8%) followed by age group of 51- 60 years (27.2%). ADRs were seen more in males (86.4%) as compared to females 13.6% and the incidence rate/ADR was higher in males. Married (93.8%) cancer patients experienced more ADR as compared to unmarried patients. Based on type of head and neck cancers, nine subsites were observed in our study. Out of this, most prevalent subsite was buccal mucosa in 122 patients (38.7%), followed by tongue in 58 patients (18%) oropharynx in 47(14.6%) patients, alveolus in 39(12.1%) patients, larynx in 32(9.9%) patients, retromolar trigone in 15 (4.6%) patients, nasopharynx in 4(1.2%) patients, metastatic (0.6%) head and neck in 2 patients and 1(0.3%) patient with lip cancer. ADR was most commonly observed in fourth stage according to TNM Staging of cancer. The prevalence of patients in IVA stage was 61.9% followed by 17.6% and 1.2% in stage IVB and IVC respectively. In IVA stage 172(53.2%) patients who received concurrent chemotherapy and radiotherapy experienced more ADR as compared to patients who received only radiotherapy (3.7%) or chemotherapy (5.6%). Similarly, in stage IVB 12.1% patients on concurrent CTRT experienced more ADR as compared to chemotherapy (5.6%). In stage IVC 1.2 % patients only on chemotherapy experienced ADR. ADR was more in patients on concurrent CTRT in stage II (3.4%) and stage III (11.5%) patients as well. Five types of chemotherapeutic drugs were administered to the patients depending on the cancer type. Cisplatin (79.2%) was the most common drug prescribed in our study as a single agent followed by carboplatin (0.6%). Docetaxel +cisplatin+ fluorouracil (7.4%), Paclitaxel +carboplatin (4.9%) and Gemcitabine + Cisplatin (0.6%) were the other common chemotherapeutic agents prescribed. In our study, majority of the patients were treated with a single drug as compared to combination drug therapy. The number of ADR was more in CTRT (n=259) group as compared to chemotherapy group (n=42). In this study, 975 ADRs of 14 types were observed in 323 patients. Among this nausea and vomiting was the most common ADR seen in 172 patients, followed by fatigue in 128 patients, mucositis in 121 patients, constipation in 92 patients, decreased appetite in 86 patients, anemia in 74 patients, hiccups in 68 patients, xerostomia in 58 patients, skin reactions in 55 patients, dysphagia in 38 patients, otic side effects in 30 patients, alopecia in 20 patients, myelosuppression in 25 patients and nephrotoxicity in 8 patients. Majority (78%) of ADR occurred in CTRT group as shown in [Table 1]. The difference in frequency of ADR was statistically significant between CTRT group compared to radiotherapy and chemotherapy group except for nausea and vomiting, mucositis, myelosuppresion and nephrotoxicity.

Table 1: Prevalence of ADR based on treatment plan

Symptom	RT (n) (% of total)	CT (n) (% of total)	CTRT (n) (% of total)	Total (n)	P-value
Nausea and vomiting	11(3.4%)	22(6.8%)	139(43%)	172	>0.05
Fatigue	0 (0%)	24 (18.8%)	104 (81.2%)	128	<0.001*
Mucositis	10(4.3%)	14(30%)	97(3.1%)	121	>0.05
Nephrotoxicity	0(0%)	0(0%)	8(2.5%)	8	>0.05
Myleosuppression	0(0%)	6(1.9%)	19(5.9%)	25	>0.05
Anemia	0 (0%)	12 (16.2%)	62 (83.8%)	74	<0.001*
Otic effects	0 (0%)	8 (26.7%)	22 (73.3%)	30	<0.001*
Skin reactions	19 (34.5%)	0 (0%)	36 (65.5%)	55	<0.001*

Alopecia	0 (0%)	12 (60%)	8 (40%)	20	<0.001*
Hiccups	0 (0%)	4 (5.9%)	64 (94.1%)	68	<0.001*
Decreased appetite	0 (0%)	8 (9.3%)	78 (90.7%)	86	<0.001*
Constipation	0 (0%)	18 (19.6%)	74 (80.4%)	92	<0.001*
Dysphagia	10 (26.3%)	0 (0%)	28 (73.7%)	38	<0.001*
Xerostomia	22 (37.9%)	0 (0%)	36 (62.1%)	58	<0.001*

[Table 2] depicts the severity of ADR and its outcome. According to Hartwig and Seigel scale, most of the ADRs were mild (63.5%) followed by moderate 29.7% and 22% were severe. Severity of ADR when compared between the CTRT, CT and RT groups, the results was statistically significant (p value<0.01) stating that severity of ADR were more when both chemotherapy and radiotherapy was given to the patients as compared to CT or RT alone. Mean score is 2.63±1.49. Median and mode score 2.

Table 2: Severity of ADR

Hartwig and Seigel level for severity					
Treatment plan	**Mild**	**Moderate**	**Severe**	**Total**	P-value
RT	21(95.5%)	1(4.5%)	0(0%)	22(100%)	<0.001*
CT	18(42.9%)	18(42.9%)	6(14.3%)	42(100%)	
CTRT	166(64.1%)	77(29.7%)	16(6.2%)	259(100%)	
Total	205(63.5%)	96(29.7%)	22(6.8%)	323(100%)	

Causality assessment was done according to WHO-UMC scale and Naranjo scale [Figure 1]. The results were statistically significant when chi square test was applied as p value was<0.01 in both scales. The mean Naranjo score is 3.08 ± 2.02 and median was 2. Definitive ADR in CTRT group is 8(1.2%) and 2(0.3%) in CT group. The most common ADR which was certain in CTRT group is anemia, fatigue and electrolyte disturbances (10) followed by nausea and vomiting (8), mucositis and diarrhea (6), constipation (4). The definitive ADR in CT group was anemia (1) and nephrotoxicity (1). The frequency of doubtful ADR is 8%, possible ADR is 58.8%, and probable ADR is 30%.

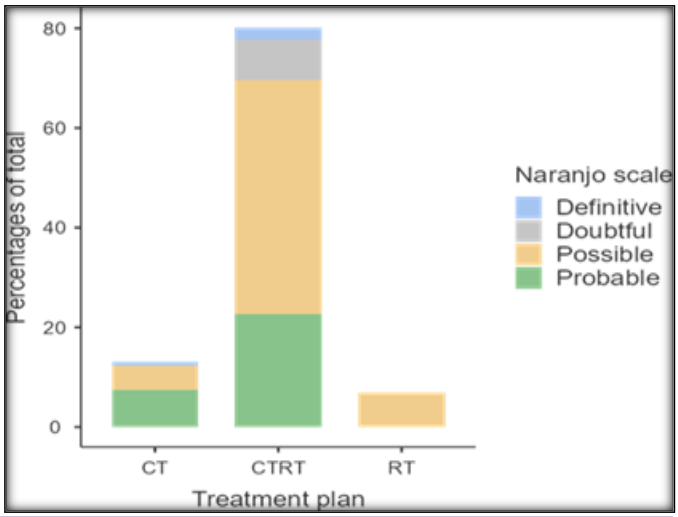

Figure 1: Frequency of causality assessment of ADR

Discussion

After the ADRs were collected and analyzed, we observed that the population belonging to the overall mean age group of 46.9±10.3 years were more prone to the development of ADR during treatment which can be compared with the study conducted by JB Wahlang et.al,[13] Poddar et.al,[14] and S.S et.al,[15] suggesting that ADRs as well as cancers are more common in this age group only. The incidence of ADR was more in male participant 86.4% as compared to female participant 13.6% in our study which can be explained by the fact that more male patients were enrolled in this study and similar findings were seen in studies done by pandit et al,[16] and Abo el Fadel et al.[17] A study from Australia reported that although males continue to have higher HNC incidence overall ,the incidence in females rose by 34% over a period 15-year period, largely attributed to increased rates of oropharyngeal squamous cell carcinoma linked to HPV.[18] The incidence of oral cavity cancers (38.7%) was higher in our study which was also reported in the studies done by Bagal et al,[2] Roy et al,[19] and Arora et al.[20] In our study 53.2% of patients receiving concurrent CTRT experienced more ADRs compared to other groups. These findings are consistent with prior study done by Liu et.al in nasopharyngeal carcinoma where patients undergoing CTRT showed significantly higher rates of severe ADRs compared to radiotherapy.[21] Similarly, research done by Lee et.al on cervical cancer showed that patients concurrent CTRT experienced a markedly higher incidence of grade ¾ toxicities (27.3%) than those receiving chemotherapy or radiotherapy alone.[22] In stage IVC, 1.2 % patients receiving only chemotherapy reported ADRs. Similarly, higher ADR prevalence was observed in patients on concurrent CTRT in stage II (3.4%) and stage III (11.5%) as well. This trend has been corroborated by clinical trials and meta-analyses showing increased risk of both acute and late toxicities in patients receiving CTRT compared to monotherapy.[23,24] These studies reinforce the current findings that concurrent administration of chemotherapy and radiotherapy significantly increases the likelihood of ADRs, especially in advanced stages such as stage IVA. Cisplatin is widely regarded as the cornerstone of concurrent chemoradiotherapy, particularly in head and neck, cervical and lung cancers, due to its radio-sensitizing properties and established efficacy. The Pignon et al,[25] showed in a metanalysis that cisplatin based concurrent chemoradiotherapy significantly improved survival in head and neck cancers but was associated with

increased toxicity. In our study also 79.2% patients were on cisplatin based concurrent chemoradiotherapy and had majority of ADRs. Similarly, Forastiere et al,[26] demonstrated that patients receiving concurrent cisplatin based chemoradiotherapy experienced more grade 3-4 toxicities than those treated with radiotherapy alone. The predominance of single-agent chemotherapy in this study aligns with real-world treatment settings where single-agent cisplatin is often favored for its tolerability and scheduling convenience. However, combination regimens like docetaxel +cisplatin+flurouracil have been used in cases of locally advanced head and neck cancers, although these are associated with higher rates of hematologic and gastrointestinal toxicities, as reported by Vermorken et al.[27] Moreover, a study by Adelstein et al,[28] found that triple-drug regimens improved control but increased adverse effects compared to cisplatin alone. The common adverse drug reaction found in this study was nausea and vomiting, fatigue and mucositis which are findings similar to most of the studies like Sharma et al,[29] who reported mucositis and nausea as the commonly occuring ADR in their study. The common ADRs reported by Pandit et al,[30] were alopecia and constipation. While constipation was common in our study, alopecia occurred in few cases. Chopra et al,[31] also showed nausea and vomiting as a common ADR followed by alopecia. Gastrointestinal system was the most affected system which was the most consisting finding in majority of studies may be because these drugs damage gastrointestinal lining, change GI motility and irritate vomiting center. Some studies reported hematologic toxicities as most common ADR as was shown by Givens et al,[32] in their study. Cooper et al,[33] reported in their study that adding chemotherapy to radiotherapy increased the occurrence of severe adverse effect which was a finding similar to our study. Although not preventable, most of the ADRs were mild in nature and were manageable with prophylaxis medicines. The causality assessment of ADRs by Kopal et al,[34] in their study revealed that most of the adverse effects (82.64%) due to chemotherapy were possible according to WHO causality assessment scale. The causality assessment of ADRs by Harshakumar et al,[35] in their study highlighted that 79% were possible whereas 21% were probable according to Naranjo scale. Our study also revealed that ADRs were mostly possible followed by probable according to Naranjo scale.

Conclusion

Concurrent chemoradiotherapy has improved the overall outcome of cancer patients but the increased adverse drug reactions cannot be ignored. Pharmacovigilance should be incorporated together with the treatment to reduce the burden of ADRs to further improve the overall outcome.

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Conflicts of interest

There are no conflicts of interest.

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