A CLINICAL STUDY ON CONCURRENT CHEMOTHERAPY-INDUCED ADVERSE DRUG REACTIONS PROFILE IN CERVICAL CANCER PATIENTS IN THE CANCER CARE UNIT

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ABSTRACT:

Background: Adverse drug reactions (ADRs) are majorly affecting the health care system in terms of decreasing quality of life and also increasing financial burden. Usage of cancer chemotherapeutic agents is associated with several Adverse drug reactions ranging from mild to severe i.e., nausea to myelosuppression.

Objectives: The Objectives of the study as follows: 1) To study the pattern of adverse drug reactions of anticancer agents in patients with cervical cancer receiving concurrent chemotherapy (carboplatin alone, carboplatin and paclitaxel combination, and radiotherapy in both therapies) in advanced or recurrent carcinoma of the cervix in patients admitted in the Oncology ward. 2) To Evaluate the Causality, Severity and preventability of the adverse drug reactions.

Methods: The study was conducted in seventy-two eligible patients with measurable advanced or recurrent cervical carcinoma were treated with carboplatin 50 mg/m2 and paclitaxel 175 mg/m2 weekly for 6 to 9 cycles or until disease progression or unacceptable toxicity. It was a Cross-sectional, Observational study conducted for 6 months in a Tertiary care cancer hospital, and 72 patients with Ca. cervix receiving concurrent chemotherapy were enrolled in this study.

Results: Overall, out of 72 patients, most common ADRs observed with these chemotherapeutic agents were nausea (32%), vomiting (21%), alopecia (12%), headache (9%), body ache (7%), anorexia (10%), diarrhea (5%), and malaise (2%) majority of the ADRs (32%) were affecting the gastro-intestinal system. ADRs most occurred in the age group of 51-61 Years is 56.93±3.54 (Mean + SD). Naranjo scale for causality assessment showed 4.16 % of the reaction to be "definite", 59.72 % to be "probable", 29.16% possible, 6.94% doubtful.

Conclusion: Carboplatin and paclitaxel in combination along with radiotherapy seems to have activity in advanced or recurrent cervical carcinoma with an acceptable toxicity profile. The use of preventive measures and active monitoring is needed and to enhance as well as reduce the incidence and severity of ADRs. This study concluded that most ADRs are preventable with active ADR monitoring.

Keywords: ADRs, Cervical cancer, Cross-sectional, Chemotherapy, Naranjo scale.

INTRODUCTION: Cancer is a main cause of morbidity and mortality in developing and developed countries. Cervical cancer is the second maximum common cancer in women in developing countries. The common causes of cervical cancer are caused by the virus Human Papilloma Virus (HPV), a sexually transmitted infection. Sexual contact is one of the cause HPV infections which lead to cancer. The most common signs and symptoms of more-advanced cervical cancer are vaginal bleeding after intercourse, between periods or after menopause, bloody vaginal discharge that may be heavy and have a foul odour, and pelvic pain.

Chemotherapy, radiotherapy, surgery, immunotherapy, biologic therapy, hormonal therapy, and cryosurgery are the diverse treatment modalities available for cancer. Chemotherapy is a significant component of treatment for many cancers, and new anti-cancer drugs represent one of the largest areas of pharmaceutical development [1].

Chemotherapy nature is usually damage cancer cells, meanwhile it also damages healthy cells, leading to side effects. Drugs most often used to treat cervical cancer include Carboplatin, Cisplatin, and Paclitaxel, 5- fluorouracil, often combinations of these are used.

Before starting the therapy Lab studies - complete blood picture, urinalysis, liver, kidney function tests, and ECG and Radiographic studies like chest X-ray, ultrasonography, CT scan, and MRI scan. The side effects of chemotherapy affect an individual's physical health, quality of life, and emotional state [2]. Radiation usually terminates cancer cells.

Although radiation damages both normal cells as well as cancer cells, the goal line of radiation therapy is to maximize the radiation dose to abnormal cancer cells while diminishing exposure to normal cells, which is adjacent to cancer cells or in the path of radiation [3].

The World Health Organization (WHO) defined pharmacovigilance as science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any drug-related problem [4]. Adverse drug reactions (ADRs) are a significant reason of morbidity and mortality, resulting in 6.5%–10.9% of hospital admissions and mortality rates of 0.15%–2.9%, and are a source of added burden to the patients in terms of economic, and the health-care systems that treat them. Cancer is direct or indirectly showing great impact on the health and socioeconomics of a nation [17].

Adverse drug reactions (ADRs) to these drugs are high compared to other classes of drugs. However, the nature of chemotherapy was damaging cancer cells while it also damages healthy cells, leading to side effects. Main side effects of chemotherapy usually affect an individual's physical health, quality of life, and emotional state. A clinical pharmacist plays a vigorous role in the early detection of these ADRs, which may help in minimizing, treating and preventing the ADRs and by either modifying the dose or changing the offending agent [5,6,13].

Along with Pharmacological management, non-pharmacological methods such as acupressure and acustimulation are good adjunct methods in treating nausea and vomiting [15].

Oncologists, radiotherapists and Onco-surgeons should be actively involved in ADR reporting as a part of Onco-pharmacovigilance, which could be a value in reduction of morbidity and mortality rates [18].

AIM AND OBJECTIVES: The present study aimed at investigating and documenting the various adverse reactions (ADRs) profile in cervical cancer patients while undergoing concurrent chemotherapy. The Objectives of the study as follows:

1) To study the pattern of adverse drug reactions of anticancer agents in patients with cervical cancer receiving concurrent chemotherapy (carboplatin alone, carboplatin and paclitaxel combination, and radiotherapy in both therapies) in advanced or recurrent carcinoma of the cervix in patients admitted in the Oncology ward.
2) To Evaluate the Causality, severity and preventability of the adverse drug reactions.

METHODOLOGY:

Study Sample- The present study was conducted among 72 women patients with cervical cancer.

Study Period- The present study was conducted for a period of 6 months, (September 2021 to March 2022).

Study Site - The present study was conducted in a tertiary care hospital in the Pragna cancer hospital, Anantapur. The study was conducted and performed after getting proper approval from the Institutional Ethics Committee.

Study design - The present study is a cross-sectional, observational study was conducted in the Oncology department after Institutional ethics committee approval.

Demographic profiles, clinical details, and prescription data were collected in specially designed proforma and analyzed after obtaining written informed consent from patients.

Study Criteria-

Inclusion criteria - Patients in the age group of 21 years and above.

Patients who receive chemotherapy between the 2nd cycle and 5th cycle, patients who undergo both radiation therapy and surgery, and patients with only cervical cancer.

Exclusion criteria- Patients who are not willing to participate in the study and were unable to respond were excluded from the study. All the female patients attending the oncology department were undertaken. Males are excluded from the present study.

Causality was assessed or evaluated using Naranjo's algorithm. Naranjo's algorithm is a questionnaire-based scale consisting of ten questions with three types of answers, yes, no, or do not know. Scores are given accordingly, based on the drug reaction can be classified as definite, probable, possible, and doubtful based on the total score.

The collected information was documented in the case record form and analyzed for demographic details, Drug details, Causality of adverse drug reactions.

A separate data entry form was prepared to record patient demographic details, stage of cancer affected, several chemotherapy cycles completed, type of chemotherapy drugs taken, suspected ADR occurrence, and category and outcome of ADR. To evaluate the causality of chemotherapy-induced ADR, the Naranjo ADR Probability Scale was used. The Naranjo ADR Probability Scale includes of ten questions that are answered as either Yes, No, or "Do not know." Unlike point values (−1, 0, +1, or +2) are assigned to each answer. The total score ranges from −4 to +13; the causality of ADR is measured as definite if the score is 9 or higher, probable if score is 5–8, possible if 1–4, and 0 or less if doubtful. The outcome of the ADR was recorded under six categories fatal, continuing, recovering, recovered, unknown, and others.

Any ADR observed by the patient or treating physician was noted in detail. The patients received cancer concurrent chemotherapy as per the treating physician's assessment. There is no change in

the treatment decision, schedule, or duration were made as a portion of the study. All the patients received pre-medication ranitidine, dexamethasone, and ondansetron in IV form to avoid emesis, as chemotherapeutic drugs are highly emetogenic drugs.

The collected information was documented in the case record form and analyzed for demographic details, drug details, causality, preventability, and severity of adverse effects. Causality was assessed by Naranjo's algorithm.

This particular study is important because of few reasons, like safety assessment, treatment optimization, patient care and support as well as research and development.

RESULTS: In this study, 72 patients were enrolled, and each patient has experienced one or the other ADR. All are female patients. The majority of the cases were seen in the age group of 51-61 years 32 (44.44%). Women patients of 61 (84.72%) were married. Most of them were housewives 41 (56.94%) while the other factors like menopausal status post menopause 49 (68.05%) and 43 (59.72%) have not taken hormonal replacement therapy. Significant improvement was found in Side B, after treatment than on Side A.

Overall treatment-related toxicity (ADRs) was more inside A than on Side B. Patients in Side A received carboplatin 50mg/mg2 in IV infusion on the first day of each treatment per week in addition to radiotherapy. Patients among Side B received carboplatin 50mg/mg2 and paclitaxel 175 mg/m2 in IV infusion on the first day of each treatment per week in addition to radiotherapy. ADRs most occurred in the age group of 51-61 Years is 56.93±3.54 (Mean + SD). As mild, moderate, or severe with various levels according to factors like a requirement for change in treatment, duration of hospital stay, and the disability produced by the adverse drug reaction.

The results of this study can help improve the overall care and treatment outcomes for cervical cancer patients in cancer care unit.

Tab -1: Demographic details of the patient

S.No	**Demographic details**	**Percentage**
1.	**Age (In Years)**	
	21-31	5.50 %
	32-41	18.05
	42-51	%
	51-61	27.70%
	>61 years	44.44%
	Total	4.16%
		99.85%
2.	Education	
	Literate	26.38%
	Illiterate	73.61%
3.	Occupation	
	Working	11.11%
	Homemaker	56.94%
	Others	31.94%

4.	Marital status Married Unmarried Divorced/Widow	 84.72% 2.7% 12.5%
5.	Menopausal Status Premenopausal Postmenopausal	 31.94% 68.05%
6.	Hormonal Replacement therapy Yes No Unknown	 29.16% 59.72% 11.11%

Fig-1: Distribution based on Stage of Disease

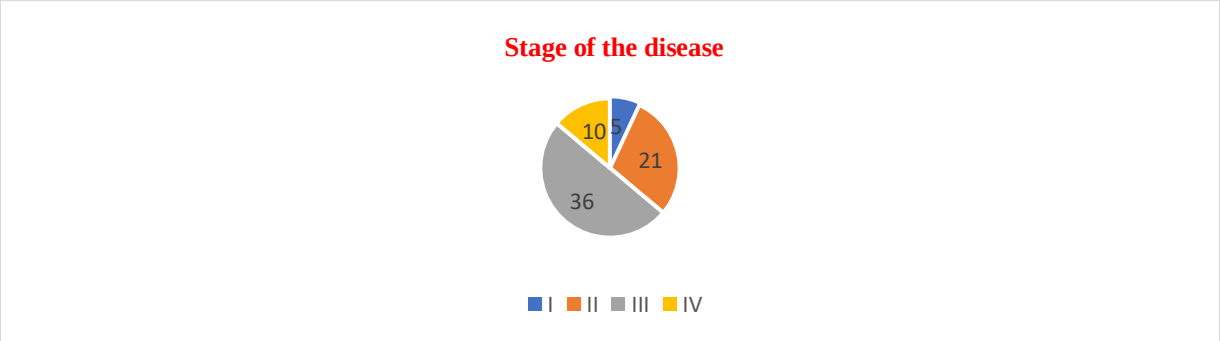

Fig-2: Distribution based on Type of Treatment received.

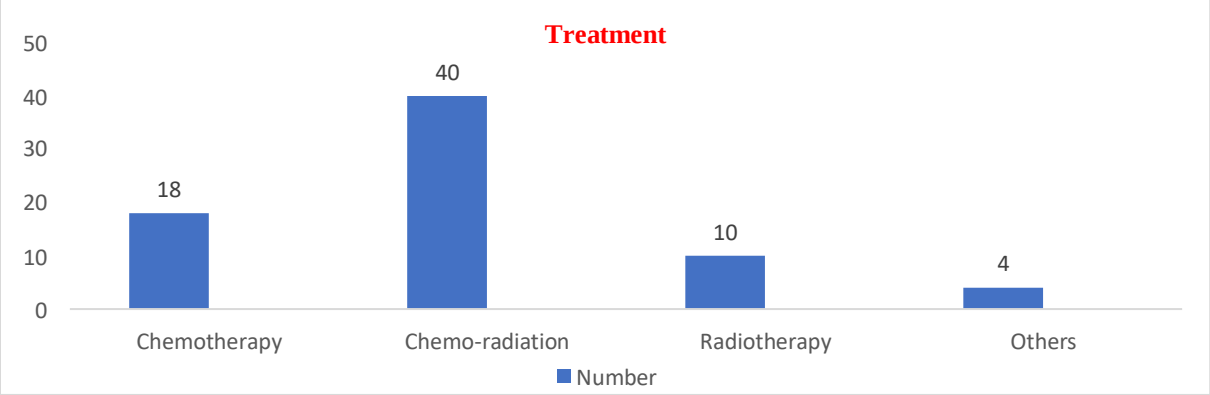

Figure 1 & 2 Indicates Stage III-36 (50%) was the most common stage diagnosed followed by stage II-21 (29.16%) and Chemoradiation treatment is high at 40 (55.5%) and 37 patients (51.38%) did not show proper interest in the completion of treatment, 26 patients (36.11%) had active treatment and 9 (12.5%) active treatment was unknown.

Tab: 2 Categorization of the system affected due to adverse drug reaction-

S.No.	Naranjo category of ADR	Percentage
1.	Definite (>9) Probable (5 to 8) Possible (1 to 4) Doubtful (<0)	4.16% 59.72% 29.16% 6.94%

Table 2 depicts the causality of ADR and its outcome. According to Naranjo's algorithm, most of the ADRs probably occurred (59.72%) followed by possible (29.16%), definite (4.16%), and 5 patients who had no ADR, which were categorized as doubtful (who had a Naranjo scale score of 6.94%).

Fig: 3 Distribution based on chemotherapeutic agents in cervical cancer patients –

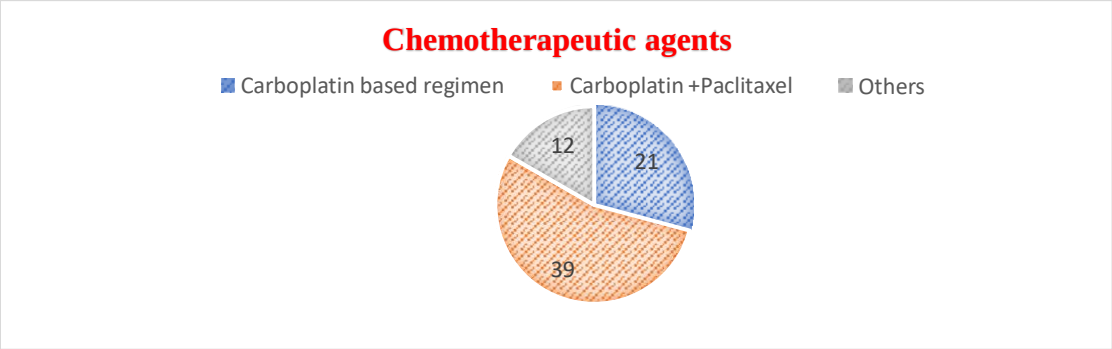

Fig: 4 Distribution based on adverse drug reactions to the affected system

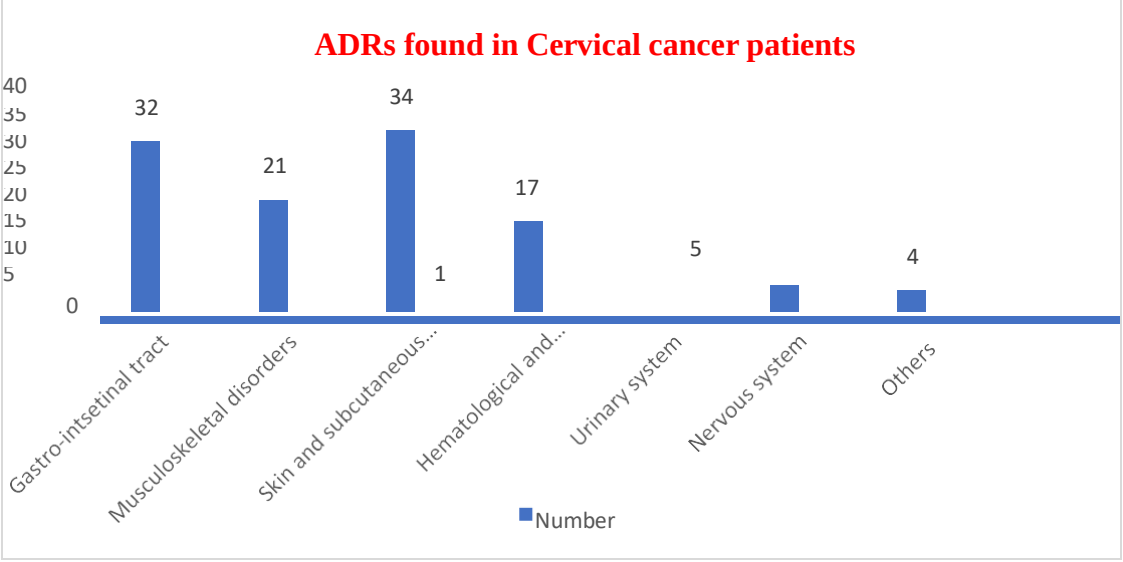

Figure 3 indicates Patients with Carboplatin + Paclitaxel are high followed by Carboplatin based regimen. Figure 4 describes the eight types of organ systems affected due to chemotherapy-induced ADR. Among them, the majorly affected system was the gastrointestinal tract (44.40%) followed by the muscular system 21 (29.16%), dermal 34 (47.20%), hematology 17 (23.60%), and nervous system 5 (6.94%), and others 4 (5.50%).

Fig: 5 Incidence of Adverse drug reactions in cervical cancer patients –

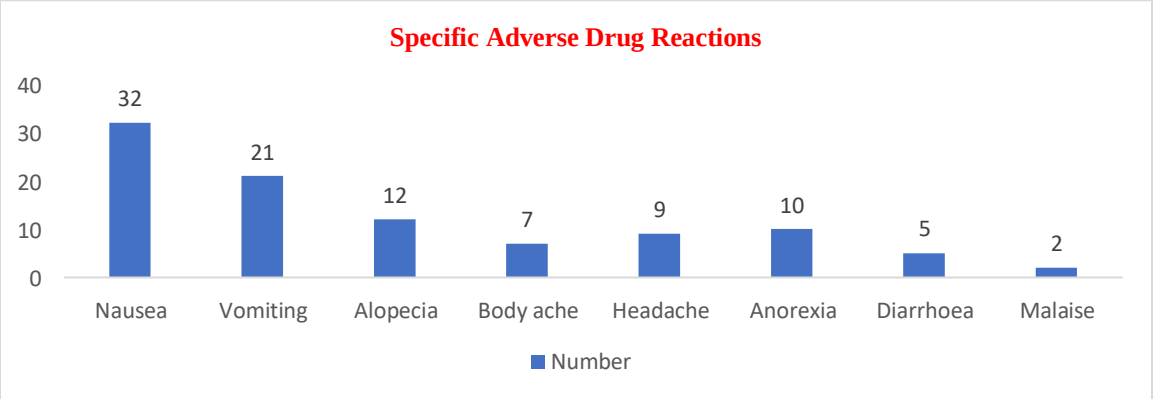

Fig- 5 Indicates the ADRs observed with these chemotherapeutic agents were nausea 32 (44.40%), vomiting 21 (29.10%), alopecia 12 (16.6%), headache 9 (12.50%), body ache 7 (9.72%), anorexia 10 (13.80%), diarrhea 5 (6.94%), and malaise 2 (2.70%).

DISCUSSION - The most frequent adverse effects include nausea, vomiting, and alopecia. The study has proved the need to improve the management of nausea and vomiting. Some of the rare reactions include headache, malaise, diarrhea, and anorexia.

Nausea and vomiting were found to be the most common ADR in our study, correlates with to the studies conducted by Kumar et al. and Keshri et al. [7,8-10] A study done by Chopra et al. was reported as the causality of ADRs was majorly possible followed by probable which was different to our study.[11]

In this study, we observed that most of the patients having alopecia as ADR i.e., (16.6% of patients) in contrast to the study of Kamil et al in which alopecia was the frequent ADR. Hair loss has been rated as one of the most distressing side effects of chemotherapy and nausea and vomiting. Most of the patients who developed alopecia 9 were on carboplatin and paclitaxel combination and only 3 were on carboplatin therapy. So, hair loss seems to be more common with carboplatin and paclitaxel combinations. 5 Diarrhoea cases were seen in 6.94% of the patients which can occur due to mucosal cell toxicity. In common the majority of ADRs were preventable.

ADRs like nausea and vomiting are very common and be effectively controlled. The possible toxicity was assessed that the treating physician should anticipate and counsel the patient effectively before initiating therapy. Chemotherapy-related nausea and vomiting remained a problem in many patients despite the use of 5-HT3 receptor antagonists and dexamethasone.

So, modification in the management of nausea and vomiting is needed very much. Most of the reactions were of mild severity and there would be no strong indication to change or withhold the

drug for mild adverse effects.

Causality was done using (NARANJO scale) and WHO scales [16]. Naranjo scale was categorized most of the ADRs probably occurred (59.72%) followed by possible (29.16%), definite (4.16%), and 5 patients had no ADR, which was categorized as doubtful (who had a Naranjo scale score of 6.94%, which correlates with our study. This is important to know because most of the ADR's in hospitalized oncology patients are predictable and at least probably preventable. This can also bring awareness about the probability of the development of ADRs by antineoplastic agents [12,14].

In the present study radiation-induced skin reactions are experienced by many patients. It is dose-dependent and might be due to the decline in stem cells function, changes in the skin endothelial cells, skin-cell necrosis, and death.

During or after radiation treatment, the usage of metallic-based topical products (zinc oxide creams or deodorants with an aluminum base) must be avoided because they might increase the surface dose to the skin. Loose-fitting clothing are suggested to be worn over the irradiated area in order prevent friction injuries. A clean and dry irradiated area should be maintained. Extreme temperatures and the use of starch-based products must be avoided as they increase the risk of infection. In our study, patients treated with radiation therapy were counseled regarding the above preventive measures.

CONCLUSION – In this study, it was observed that patients with carcinoma cervix treated with concurrent chemoradiotherapy were effective for symptomatic improvement and suitable with acceptable toxicity for advanced cancer of cervical cancer than those with radiation only. Among patients with Ca Cervix, Carboplatin and Paclitaxel were the most prescribed drugs. Finally, to conclude, In the present study, carboplatin and paclitaxel was the most used chemotherapeutic agent for cervical cancer and nausea was the most common ADR which is of mild severity. Thus, the present study emphasizes the need to improve the management of ADR and pharmacovigilance for better outcomes of cervical cancer treatment in the future.

LIMITATIONS-

There is a need for vigilant ADR monitoring and reporting to decrease morbidity and mortality due to ADRs, which requires further studies on a larger population.

Time duration of this study was only for 6 months period. It requires more time period to do it in a large population.

RECOMMENDATIONS: The use of preventive measures and early detection of adverse drug reactions has the potential to reduce the severity of ADRs. Our study highlighted the importance of clinical pharmacists in the oncology department by counseling the patient regarding the early signs and symptoms, adverse effects of various treatment modalities, its identification and management, and also finding a few medication errors regarding anti-neoplastic agents.

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CONFLICT OF INTEREST -None declared
ETHICAL APPROVAL- The study was approved by Institutional Ethics Committee.

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