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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Original Research Article

Drug related problems among cervical cancer patients: A prospective study

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Abstract

Background: Drug-related problems (DRPs) are defined as drug-related events that interfere, either directly or indirectly, with the patient receiving the best possible medical care.
Aim and Objective: Study is performed to assess the drug related problems in cancer treatment of women with uterine cervix carcinoma.
Materials and Methods: A prospective study was carried out in women aged 20-79 years were examined who were receiving for chemotherapy uterine cervix carcinoma on weekly basis at Indrayani Hospital and Cancer Institute to look at drug-related issues.
Results: 54 patients had a total of 365 drug related problems (DRPs) identified. The most common DRPs were medication interactions (136, 37.26%), adverse drug responses (201, 55.06%), and non-adherence to treatment (14, 3.83%). ADRs including leucopenia, anemia, nausea, vomiting, and fatigue were the most frequent.
Conclusion: The most common DRPs were drug interactions, adverse drug reactions, and the requirement for laboratory monitoring. Adequate oversight and execution of clinical pharmacy services will undoubtedly aid in the optimization of drug-related issues.

Keywords: Uterine cervix carcinoma, Carboplatin, Drug related problems, Drug interactions and adverse drug reaction.

Received: 11-05-2024; **Accepted:** 04-11-2024; **Available Online**: 28-05-2025

1. Introduction

Medications have significantly improved health during last few decades thus decreasing the mortality. It is interesting to note that there is lot of research done and ongoing whether the right drug is being reached to the patient or not. Drug-related problems (DRPs) are drug-related events that actually or potentially impede a patient's ability to receive the best possible medical care. They are linked to patient harm and increased financial burden. DRPs are significant issues in healthcare systems across the globe. Most cancer treatment regimens are complex and very toxic therefore DRPs have enormous potential in chemotherapy.

There are 2972.8 million women in the world who are 15 years of age or older and who could have cervical cancer. Asia's highest incidence rate of cervical cancer was recorded in India (27.7%).[1,2] A woman's cervix, or the opening from the vagina into the uterus, is where cervical cancer begins to grow. Nearly all occurrences of cervical cancer (99%) are associated with high risk human papillomavirus (HPV), a virus that is widely spread through sexual contact.[3] The majority of occurrences happen in less developed nations without access to reliable screening programs. The most prevalent histological subtypes of cervical malignancies are squamous cell carcinoma and adenocarcinoma, which together account for around 70% and 25% of all cases, respectively.[4-8] Human papillomavirus exposure, smoking, sexual behavior, menstruation and sexual hygiene and immune-system dysfunction are risk factors. The lifetime risk of cancer is expected to be reduced by 25–36% in underdeveloped nations if women are screened once in their lifetime (at age 35) using a streamlined technique that involves visual inspection of the cervix with acetic acid or HPV testing in cervical cell samples. In the rural and

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https://doi.org/10.18231/j.ijogr.2025.054

underdeveloped regions of western India, there is significant clinical need to detect issues brought on by cancer therapy in cervical cancer patients in order to address this issue. Furthermore, although chemotherapy medicines are anticipated to cause worse side effects in the patients, it is unknown that how often DRPs are affecting the rural western India patients. To overcome these obstacles, it was necessary to conduct a study in order to discover DRPs in patients with cervical cancer.

2. Materials and Methods

2.1. Study design

This prospective study was conducted from November 2022 to April 2023 at Indrayani Hospital and Cancer Institute, Alandi, Pune, Maharashtra, India. It has 100 beds capacity consisting of 10 Intensive Care Unit (ICU) beds.

2.2 Study participants

The analysis of our study included women aged 20 year and above who were admitted in in-patient services. However patients with age group 0 to 20 years including above 80 years and pregnant and lactating women were not included in this study. Patients who were discharged and subsequently readmitted were assessed as new patients.

2.3. Documents prepared

A data collection form, patient information sheet and informed consent form was designed in Standard English language and translated to local language (Marathi) then back translated into English language to check the consistency. Translation of all the documents was done by certified translator.

2.4. Data analysis

A well designed data collection form was used to gather important details about each patient, including their socio-demographics, the histological types of cervical cancer, their history of sexual activity, their stage of cancer, the types of co-morbidities, their treatment plan, their menstrual history, their hormonal history and their drug-related issues. Using WHO cancer pain management protocols and National Compressive Cancer Network (NCCN) practice guidelines for cervical cancer treatment, the effectiveness of medicinal therapy was assessed.[9,10] A combination of Micromedex, Medscape, and Drugs.com was used to determine the likelihood of a drug interaction. The Cipolle et al. classification system was used to classify DRPs, which included the following: the need for additional drug therapy; the use of medication without a prescription; improper drug selection; overdosage; sub therapeutic dosage; adverse drug reactions; drug interactions; inappropriate laboratory monitoring; and patient non-adherence.[11] STATA version 17.0 statistical software was used to evaluate the data after it was entered into a Microsoft Excel worksheet. The categorical variables of the patient's characteristics were summarized using descriptive statistics like percent and frequency.

2.5. Ethical considerations

The protocol for the study was approved by head of the institute that is Indrayani Hospital and Cancer Institute. Patient information sheet was given to patient and their relatives then written informed consent was taken from all the participants of the study.

3. Results

Of the 54 patients in the study, 21 (38.88%) were between the ages of 50 and 60, while the remaining 5 (9.25%) were between the ages of 70 and 80. 53 ± 10 years was found to be the mean age. Taking missary, chewing tobacco, and bidi smokers were among the social habits seen in 10 (18.51%), 8 (14.81%), and 1 (1.85%) individuals, respectively. With a proportion of 28.81%, hypertension was found to be the most prevalent comorbidity, whereas tuberculosis and thyroid disease had the lowest percentages, at 1.69% each. Every woman was married, and forty-three (79.62%) of them were married before turning eighteen. Of the fifty-four women, eighteen (33.33%) had two children, seventeen (31.48%) had three, and two (3.70%) had more than five.

Prior to receiving a cervical cancer diagnosis, patients presented to the hospital with a variety of problems. As seen in **Figure 1**, about 27 patients (22.3%) experienced vaginal bleeding, 16 patients (13.22%) had white discharge, and 18 patients (14.87%) complained of abdominal pain, which was followed by 7 patients (5.78%) who complained of pelvic pain.

Four histological forms of cervical cancer were found in the study participants, as shown in **Figure 2**. The most prevalent histological type was 35 (66.1%) modified differentiated squamous cell carcinoma, followed by poorly differentiated squamous cell carcinoma (17 (30.4%). Cell differentiated carcinoma and adenocarcinoma 1 (1.85%) were the least common histological forms. According to the study, the most common stages were III C 14 (25%) and III B 17 (33.9%). **Figure 1** illustrates the low prevalence rates of 1 (1.8%) for stages IA, I B, and IVB.

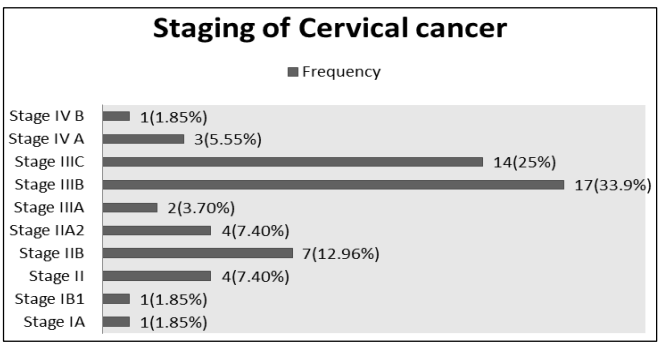

Figure 1: Staging of cervical cancer

The majority of patients were receiving cisplatin monotherapy, which had the highest percentage 37 (68.51%), followed by methotrexate with 5 FU, 15 (27.77%), and 1 (1.85%) with carboplatin and paclitaxel in **Figure 2**.

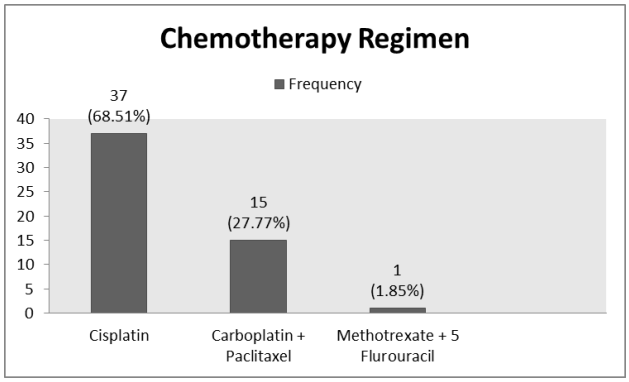

Figure 2: Chemotherapy regimen used

A total of 365 drug-related problems were found. In this study, the most common DRPs were adverse drug reactions, drug-drug interactions, and inadequate laboratory monitoring, with frequencies and percentages of 201 (55.06%), 136 (37.26%), and 12 (3.28%), respectively **Table 1**.

Table 1: Type of DRPs

DRPs	Frequency	Percentage (%)
Drug-drug interactions	136	37.26%
Adverse Drug Reactions	201	55.06%
Sub-therapeutic dosage	3	0.82%
Over dosage	2	0.54%
Non Adherence	11	3.01%
Inadequate Laboratory monitoring	12	3.28%

Among research participants, 136 drug-drug interactions were found. 12 (8.82%) of the drug interactions were substantial, necessitating changes or careful observation of how the drug interactions turned out **Table 2**.

Table 2: Monitoring drug interactions

S. No.	Drug	Interacting drug	Effect	Frequency	Percentage (%)
1	Amlodipine	Metformin	Amlodipine lessens the effects of metformin (BSL monitoring)	1	8.33
2	Mefenamic acid	Dexamethasone	Increases mutual toxicity through synergism	1	8.33
3	Diclofenac	Dexamethasone	Increases mutual toxicity through synergism	2	16.66
4	Ondansetron	Metformin	Ondansetron reduces the effects of metformin	1	8.33
5	Aspirin	Potassium chloride	Raises the potassium level (check the K level)	1	8.33
6	Ferrous Sulphate	Dolutegravir	Dolutegravir level or action will be lowered by ferrous sulfate through cation binding in the GI tract.	1	8.33
7	Mefenamic acid	Potassium chloride	Serum potassium levels (monitor K level) rise with both.	1	8.33
8	Ferrous Sulphate	Pantoprazole	Pantoprazole raises the pH of the stomach, which reduces the amount or impact of ferrous sulfate.	1	8.33
9	Diclofenac	Hydrocortisone	Increases mutual toxicity through synergism	2	16.66
10	Dexamethasone	Doxorubicin liposomal	Dexamethasone will lessen its impact.	1	8.33

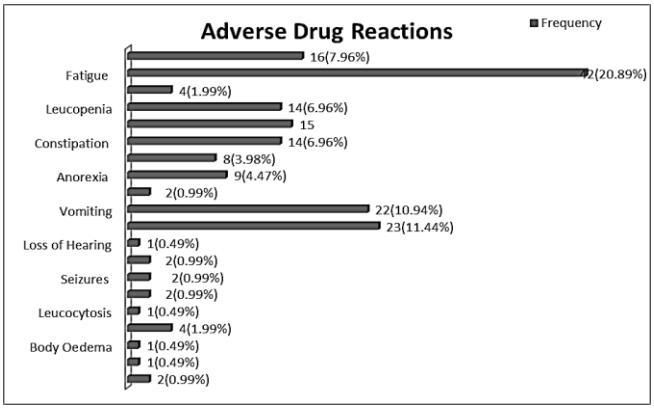

Figure 3: Adverse drug reactions

Fatigue, nausea, and vomiting accounted for 42 (20.89%), 23 (11.44%), and 10 (10.94%) of the 201 ADRs found in this study, making them the most common. However, as **Figure 3** illustrates, fever, edema, leukocytosis, and hearing loss were the least common ADRs.

4. Discussion

This study outlines the entire process of evaluating medication-related issues in patients with uterine cervical carcinoma, which is carried out by a group of clinical pharmacists working under the direction of physicians. Drug-related issues constitute serious healthcare issues, many of which are avoidable. It includes gathering data from the hospital's chemotherapy ward. The majority of the women included in this study were 53±10 years old. This figure may be explained by the high incidence of human papillomavirus and the low immunization rate in poor nations. It can be as a result of the women in those nations not getting regular screenings. The research population's mean age was 53.3±11.6 years, 50.2±10.7 years, and 52.24±8.66 years in the studies by Degu A et al, Kefale B et al, and Jire AS et al.[12-14]

This result is consistent with an Iranian study that found that among patients with cervical cancer, anemia was the most common consequence, occurring in 59.0% of cases.[15] The second most common kind of co-morbidity in patients with cervical cancer was retroviral illness (18.3%). In Zimbabwe, a cross-sectional study revealed that 25.6% of individuals had a retroviral illness.[17] Furthermore, a number of studies have demonstrated a robust correlation between HIV infection and cervical cancer, with a high frequency of high-risk HPV DNA in HIV-positive women.[18,19]

Among the study participants, four histological forms of cervical cancer were found. On the other hand, three histological types of cervical cancer were identified in the study done in Kenya. Squamous cell carcinoma (modified differentiated) was the most common type, with 35 (66.1%) followed by squamous cell carcinoma (poorly differentiated) with 17 (30.4%). Cell differentiated carcinoma and adenocarcinoma, with 1 (1.85%), were the least common histological types. The most frequent histological type was squamous cell carcinoma (91.4%), which was followed by adenocarcinoma (7.4%), while the least common kind was invasive anaplastic carcinoma (1.2%). Adenocarcinoma (7.1%) was the most prevalent form, while squamous cell carcinoma (88.6%) was the most common.

According to this survey, the most common stages were IIIB 19 (33.9%) and IIIC 14 (25%) respectively. On the other hand, the prevalence rates for stages IA, IB, and IVB were only 1 (1.8%) apiece. According to a study conducted in Kenya, stage II and stage III cervical cancer affected 44.4% and 35.8% of the sample population, respectively, with stages IIB (33.3%) and IIIB (28.4%) having the highest prevalence. Nonetheless, the prevalence rates for stages I and IV were low.[12] In contrast, stage II and stage III cancer were found in 38.6% and 40.2% of the study group, respectively, according to a study by Kefale B et al. Furthermore, the patients' rates of recurrence and metastasis were 10.9% and 16.3%, respectively.[13] The way the disease was progressing, the death rate in our environment was extremely high beyond stage IIIB. Furthermore, a large percentage of patients with severe disease stages were transferred to more sophisticated treatment centers.

The majority of the patients were receiving cisplatin monotherapy, which has the highest percentage of 37 (68.51%). This was followed by methotrexate with 5 FU, 15 (27.77%), and 1 (1.85%) with carboplatin and paclitaxel. In contrast, cisplatin and paclitaxel 9 (11.1%) were the most often utilized combination anticancer drugs in the treatment of cervical cancer, according to the study by Degu A et al.[12] In contrast, the Kefale B et al. study found that the least prescribed treatment regimen involved a combination of leucovorin, 5 FU, and oxaliplatin.[13] The proportion of anticancer medications provided in the Jire AS et al. trial was cisplatin (72%), paclitaxel (40%), 5 FU (36%), carboplatin (32%), and gemcitabin (4%).[14]

The most widely used preventive antiemetic regimen was combination 51 (37.77%) consisting of dexamethasone and granisetron. On the other hand, granisetron and dexamethasone monotherapy was less commonly used in the management of chemotherapy-induced emesis among the study participants. This is similar to the findings of a study by Degu A et al, where the most often used prophylactic antiemetic regimen was granisetron and dexamethasone combination 32 (39.5%), followed by a combination of ondansetron and dexamethasone 18 (22.2%).[12] According to a study by Kefale B et al., the most often utilized prophylactic regimen combination was metoclopramide and dexamethasone combination 58 (31.5%), which was followed by a combination of ondansetron and dexamethasone 38 (20.7%).[13]

In this study, 54 individuals with uterine cervix cancer had 365 drug-related issues investigated. The most common DRPs in this study were adverse drug reactions, drug-drug

interactions, and inadequate laboratory monitoring, with frequencies and percentages of 201 (55.06%), 136 (37.26%), and 12 (3.28%). Degu A et al, found 215 DRPs overall from 76 patients with cervical cancer, which translates to a prevalence of 93.8%. The most common DRPs, accounting for 56 (69.1%), 38 (46.9%), and 32 (39.5%) cases, respectively, were adverse medication responses, drug interactions, and the requirement for additional drug therapy.[12] In contrast, DDI was not the most common DRPs detected in the study by Mustapha S et al, but rather, about 26.98% of DRPs were identified from 65 patients. This study is similar to the one conducted here in that a significant portion of DRPs identified were adverse drug reactions (ADRs), which had the highest percentage (29.02%) with regard to the problems type and were primarily associated with chemotherapeutic agents.[16]

A quarter of the DDIs had considerable severity, meaning that they needed to be modified or the results of the medication interactions needed to be closely watched. Twelve (8.82%) of the DDIs, however, were severe enough to require monitoring or the addition of other drugs to the treatment plan. According to our research, a number of medication combinations taken by patients, including granisetron and ondansetron, which lengthen the QTc interval, may be to blame for the occurrence of DDI. In addition to causing withdrawal symptoms such irritability, mood swings, despair, anxiety, and insomnia in patients who are already opiate addicted, tramadol and diphenoxylate HCl together have the potential to rekindle opiate dependence in individuals.

Certain medications, such as mefenamic acid and dexamethasone, and diclofenac and dexamethasone, augment each other's toxicity in a synergistic way. This interaction led to the conclusion that when given jointly, steroids and NSAIDs need to be continuously monitored. Dexamethasone with paclitaxel, where in the latter may lessen paclitaxel's effects and blood levels. Dexamethasone will raise paclitaxel's concentrations or effects. When given with a CYP2C8 inhibitor, paclitaxel levels or toxicity may rise. Patients with cancer typically have co-morbid conditions and need to take numerous additional drugs. The majority of patients with comorbid conditions like diabetes mellitus and hypertension are taking metformin and amlodipine, respectively. Patients taking ondansetron with metformin and amlodipine with metformin needed to have their blood sugar levels monitored.

The study detected 201 ADRs, of which fatigue, nausea, and vomiting accounted for 42 (20.89%), 23 (11.44%), and 10 (10.94%) of all cases, respectively. The least prevailing ADRs were loss of hearing, leukemia, edema and fever. Of the 166 ADRs identified in the study conducted by Degu A et al, the most common were vomiting, nausea, and leucopenia which accounted for 40(49.4%), 24(29.6%), and 18(22.2%) respectively which was similar in 59 ADRs identified by Kefale B et al, the most common were vomiting (51.2%), nausea (43.7%), and leucopenia (37.1%).[12,13] While baldness (32%), headache (12%), bodyache (12%), anorexia (12%), diarrhea (8%), and malaise (4%), Jire AS et al. noted ADRs with chemotherapeutic drugs included nausea (76%), vomiting (40%), and atrophy (32%).[14]

ADRs associated with chemotherapy are closely related to the treatment itself. Since most cytotoxic drugs are unable to distinguish between cancerous and healthy cells, the majority of adverse drug reactions appear to be unavoidable. Cytotoxic drugs have a complicated pharmacologic profile and a limited therapeutic window. Pharmacokinetic parameters in cancer ward patients may be affected by the illness process itself, as well as by malnourishment, decreased serum-binding protein levels, edema, and/or renal and/or hepatic dysfunction. Drug interactions therefore pose a greater risk to cancer cases.

5. Conclusion

Patients in cancer wards are the most susceptible population, with a higher likelihood of drug-related issues. The most common DRPs were drug interactions, adverse drug reactions, and the requirement for laboratory monitoring after the acceptance of this problems proper monitoring was done. In developing country like India proper monitoring and implementation of clinical pharmacy services is still at infancy stage thus accepting it will definitely help to optimize and drug related problems.

6. Source of Funding

There was no funding used for this research.

7. Conflict of Interest

There is no conflict of interest declared by the authors.

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Cite this article: Khaire AH, Patel EA, Savane SA, Shinde AS, Kumbhar AR, Pathan A. Drug related problems among cervical cancer patients: A prospective study. *Indian J Obstet Gynecol Res*. 2025;12(2):318–323.