

Research Article



Drug Utilization Study and Adverse Drug Reactions Profile of Drugs in Patients of Ovarian Cancer in Tertiary Care Teaching Hospital

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ABSTRACT

Ovarian cancer is one of the most common gynaecologic cancers. Concerns pertaining to major health burden on society can be reduced by drug utilization study which gives an idea for detecting early signals of irrational drug use. This cross-sectional observational study aims at analyzing utilization pattern of drugs and Adverse drug reactions in the treatment of ovarian cancer at a tertiary care hospital in perspective of standard treatment guidelines. 170 patients of Ovarian Cancer receiving chemotherapy were enrolled in study after written informed consent of patients. Approval was obtained from institutional ethics committee. It was cross-sectional, observational study. Prescriptions were analysed for number of drugs prescribed using a predesigned format. Any Adverse Drug Reaction (ADR) observed by patient or treating physician was noted and causality was assessed by Naranjo's algorithm. Preventability and severity of ADRs were assessed by modified Schumock and Thornton scale, modified Hartwig and Siegel scale respectively. In our study, ovarian cancer was encountered maximum in age group of 60-80 years. Most commonly prescribed chemotherapeutic drug was Paclitaxel (96.47%). Causality assessment of ADR by Naranjo's algorithm showed 45.56% definite, 29.9% probable and 24.54% possible reactions. According to modified Schumock and Thornton scale, 30.73% reactions are 'not preventable', 5.36% are probably preventable, 63.91% are 'definitely preventable'. According to modified Hartwig and Siegel scale, 51.96% were 'mild' severity however 48.04% were 'moderate' severity.

Keywords: Ovarian cancer, Adverse Drug Reaction (ADR), Paclitaxel, Chemotherapy- drug utilization, prescription pattern study.

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INTRODUCTION

Drug utilization research has been defined by the World Health Organisation (WHO) in 1977 as —the marketing, distribution, prescription and use of drugs in society, with special emphasis on the resulting medical, social and economic consequences. Drug utilization is an important component of many research initiatives that examine the clinical and economic effectiveness of pharmacotherapy.^{1,2} According to WHO definition, Adverse Drug Reactions (ADR) is “Any response to a drug which is harmful, inadvertent and occurs at doses used in man for prophylaxis, diagnosis or therapy.”³ A study conducted in the USA revealed that adverse drug events extended the hospital stay, increased the cost of hospitalization and nearly two-fold increased risk of death.⁴ Most commonly occurring ADRs with anticancer drugs include alopecia, oral ulceration, anorexia, nausea,

vomiting, diarrhoea, low blood counts. The lifetime risk for epithelial ovarian cancer is 1.38% or 1 in every 72 women. The risk further increases in women with familial and genetic predisposition to this disease.⁵ Epithelial ovarian cancer are the most common ovarian cancers accounting for approximately 90% of ovarian cancer. The most common sub-type of epithelial ovarian cancer, the high grade serous lesion most commonly arises from the fimbriated end of the fallopian tubes and is associated with mutation in Breast Cancer genes [BRCA1 or BRCA2] in 10% to 15% of cases.⁵ Currently, standard treatment is a staging and debulking laparotomy followed by platinum-based chemotherapy. A meta-analysis of 6962 women found that a 10% increase in the rate of maximal debulking surgery improved the median survival by 5.8%.⁶ The first-line chemotherapeutic regimen for late stage epithelial ovarian cancer is paclitaxel in combination to carboplatin. However, in most of cases, relapse occurs within six months despite the initial success of this chemotherapeutic combination. A lot of challenges have been encountered with the conventional delivery of paclitaxel in addition to the occurrence of severe off-target toxicity. Another obstacle is the multi drug resistance which is the main cause of Ovarian Cancer recurrence.⁷ These hurdles in pharmacotherapy can be overcome by periodic evaluation of drug utilization and optimizing



prescription pattern by forming prescription guidelines for ovarian cancer patients. Much of the documented evidence on drug utilization pattern and ADRs come from developed countries. There is need for effective pharmacovigilance in India owing to absence of Indian data on adverse effects and the genetic diversity of the Indian population. Hence this study was planned to study prescription patterns in ovarian cancer patients, analyse ADRs, its causality, severity and preventability in patients of ovarian cancer.

MATERIALS AND METHODS

This is a cross sectional and an observational study undertaken from December 2017- august 2019 in tertiary care teaching institute in India. The study protocol was approved by the Institutional Ethics Committee prior to the commencement of the study and was carried out in accordance with Good Clinical Practice guidelines & ethical principles as mentioned in Declaration of Helsinki. Written informed consent was taken from the patients who were willing to participate in the study. Totally, 170 patients from the department of Radiation and Oncology were included in the study.⁸ Women suffering from ovarian cancer above the age of 18 years were included in the study. Patients suffering from any other malignancy and those receiving first cycle of chemotherapy were excluded from the study. Prescriptions were collected from patients who attended out-patient department of Radiotherapy and Oncology in the hospital and those who were admitted in day care ward of Radiotherapy and Oncology of the hospital. Patient's prescription sheet was evaluated and name, age, address, education, weight, investigations and co-morbid conditions were looked for. Analysis was carried out in a pre-validated self-designed proforma for the names of drug prescribed, total number of drugs prescribed, average number of drugs per prescription, use of fixed dose combinations (FDC), whether drugs were included in National List of Essential Medicines (NLEM). The route of administration, formulation and dose of drugs were analysed. Brand and generic names of drugs with the frequency of administration of drugs were also noted. The patients and the relatives were asked for occurrence of any adverse drug reactions after the administration of chemotherapy. Immediate adverse drug reactions were asked to the patients soon after she received her chemotherapy cycle. Patient was also enquired for late adverse drug reaction if occurred after the previous chemotherapy cycle. Adverse drug reactions if noted by the treating physician or investigator were also asked.

ADRs observed were noted in Central Drugs Standard Control Organisation (CDSCO) ADR reporting form. Causality assessment of ADRs were done by Naranjo's algorithm.⁹ Preventability was assessed by modified Schumock and Thornton scale.¹⁰ Severity of ADRs were assessed by modified Hartwig and Siegel scale.¹¹ Confidentiality of the information was assured through out the study.

Sample Size Calculation

Total 170 patients were enrolled in the study. Prevalence of the most commonly prescribed drugs was taken as 88% from the previous pilot study with Precision 5% and confidence interval as 95%. After putting all these values in sampsiz.sourceforge.net software, the sample size came out to be 162 and was rounded to 170.⁸

Statistical Analysis

Descriptive statistics was used to analyse data for demographic parameters. Results are expressed as percentage frequency and Mean \pm SD or median, depending on whether the data is parametric/non-parametric.

RESULTS

Demographic profile is shown in Table 1. Majority of patients were in the age group of 60-80 years of age. Maximum females weighed between 35- 60 kilograms. Most of the females were underweight and undernourished.

Table 1: Demographic profile of cases in ovarian cancer [n=170]

Parameter	Observations
Average age (years)	64.26 \pm 15.43
Average weight (kilogram)	46.22 \pm 10.72
Education - Illiterate	67.64%
- Up to 10 th standard	17.64%
- Graduate	14.72%

Values are expressed as mean \pm SD

Ten most commonly prescribed chemotherapeutic drugs in ovarian cancer are shown in Figure 1 of which Paclitaxel 240 mg was most frequently prescribed drug (164 prescriptions), followed by Carboplatin 450 mg (157 prescriptions) and Cisplatin 25 mg (24 prescriptions).

All of the patients prescribed with chemotherapeutic drugs in ovarian cancer were simultaneously treated with adjuvant drugs as shown in Figure 2. Intravenous Ondansetron, Ranitidine, Dexamethasone, Oral Ferrous sulphate folic acid tablets, oral Multivitamin and B Complex supplementation was prescribed to all the patients. This was followed by oral Paracetamol tablets (55 prescriptions) and oral Tramadol tablets (55 prescriptions)

Eleven most commonly encountered adverse drug reactions to chemotherapeutic drugs in ovarian cancer are shown in Figure 3. Alopecia was the most commonly encountered ADR (145 patients) followed by Nausea (113 patients), Vomiting (108 patients) and Tingling (34 patients). Least commonly observed ADR was pigmentation of tongue (four patients).



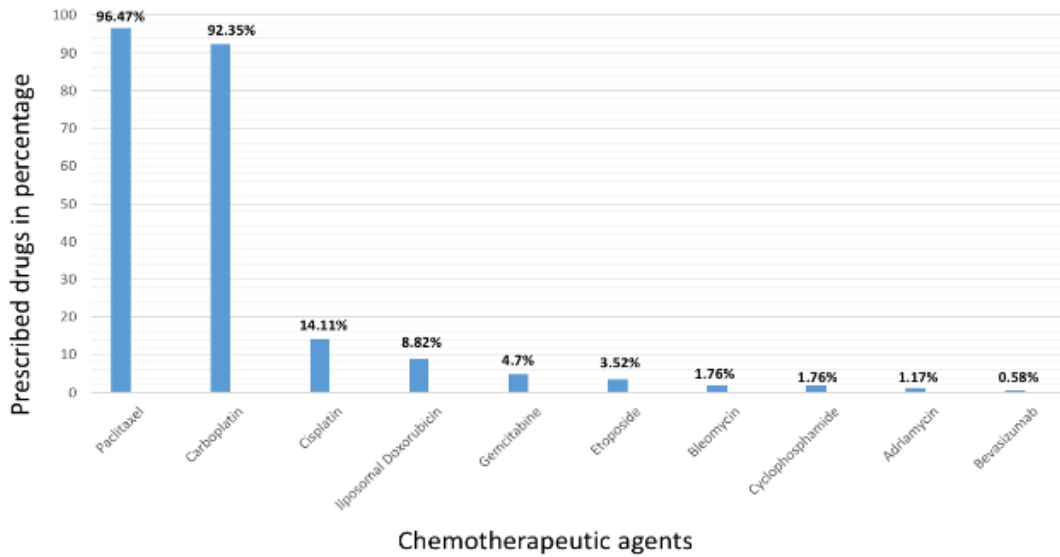


Figure 1: Drug utilization pattern of chemotherapeutic agents in ovarian cancer [n=170]

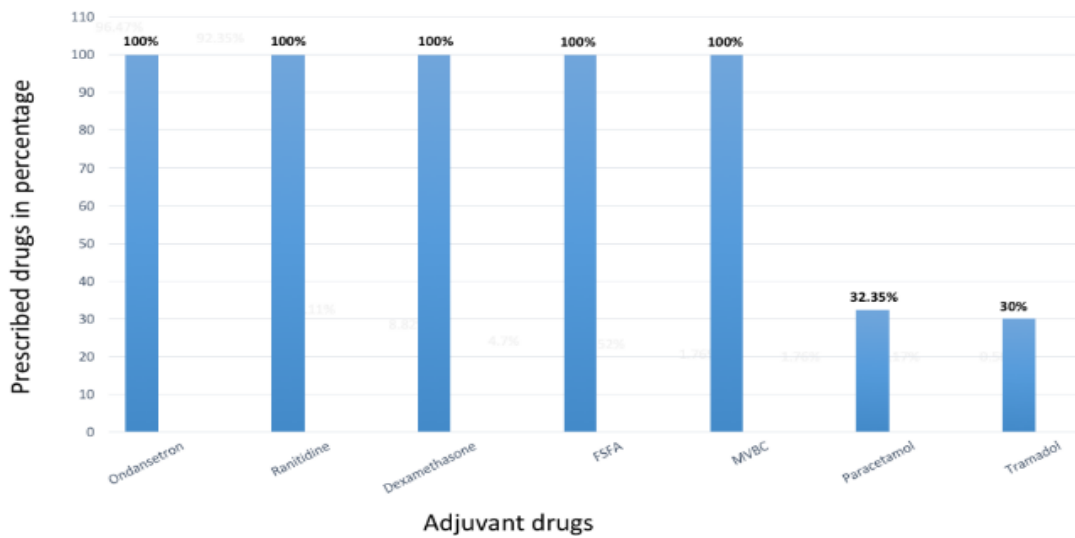


Figure 2: Drug utilization pattern of adjuvant drugs in ovarian cancer (n=170)

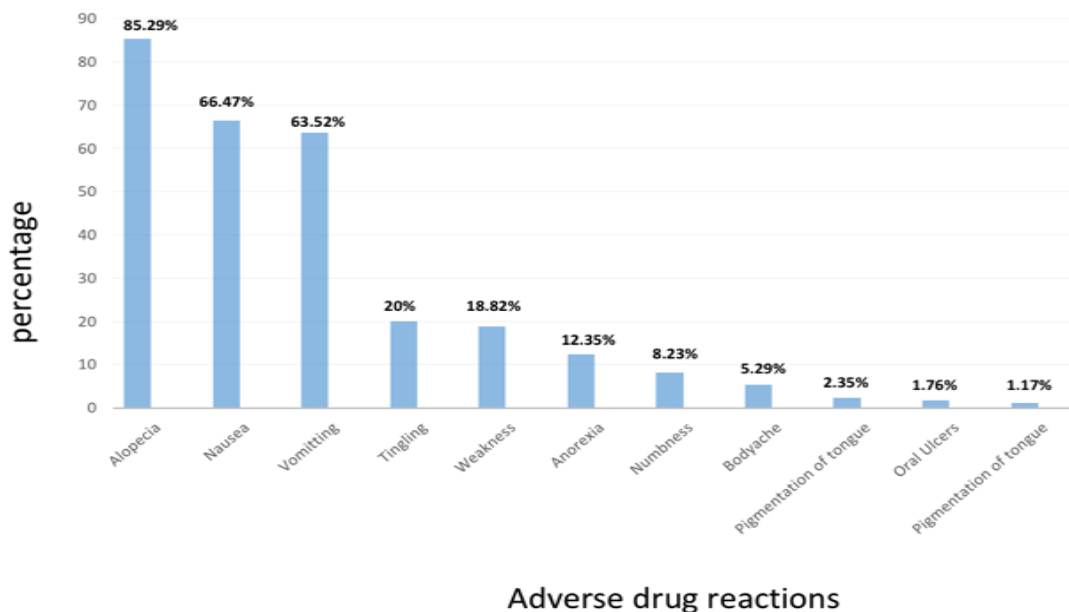


Figure 3: Adverse drug reaction profile of chemotherapeutic agents in ovarian cancer (n=170)



Analysis of routes of administration for Chemotherapeutic agents in Ovarian cancer [n=170]

- All the chemotherapeutic agents were administered in parenteral route to all the ovarian patients included in the study

Adjuvant treatment given to prevent ADRs in ovarian cancer [n=170]

- Every patient included in the study was adequately premedicated with Parenteral Dexamethasone [Corticosteroid], Ranitidine [H2-receptor antagonists], Ondansetron / Granisetron [Serotonin 5-HT₃ receptor antagonist], Ferrous sulphate tablets, Multivitamin tablets, Analgesics like tablet Tramadol and Antipyretics like tablet Paracetamol.

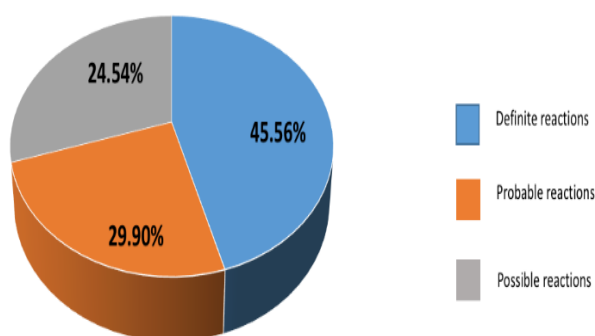


Figure 4: Causality Assessment of ADRs by Naranjo's Algorithm in ovarian cancer [n=170]

Causality Assessment of ADRs by Naranjo's Algorithm in Ovarian cancer revealed maximum reactions to be definite (221 out of 485 reactions) followed by probable (145 out of 485 reactions) and possible (119 out of 485 reactions).

Definitely Preventable	Probably Preventable	Not Preventable
63.91%	5.36%	30.73%

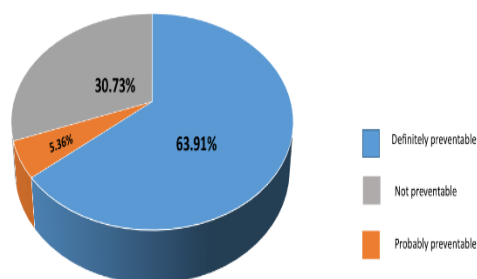


Figure 5: Preventability Assessment of ADRs by Modified Schumock and Thornton scale in Ovarian cancer [n=170]

Preventability Assessment of ADRs by Modified Schumock and Thornton scale in Ovarian cancer revealed maximum reactions to be definitely preventable (310 out of 485 reactions) followed by not preventable (149 out of 485 reactions) and probably preventable (26 out of 485 reactions)

Mild	Moderate	Severe
51.96%	48.04%	0%

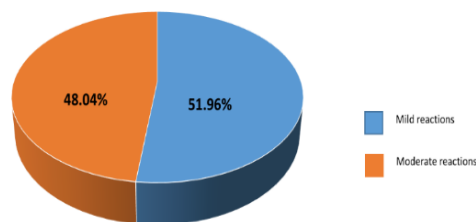


Figure 6: Severity assessment of ADRs by Modified Hartwig and Siegel scale in Ovarian cancer [n=170]

Severity assessment of ADRs by Modified Hartwig and Siegel scale in Ovarian cancer revealed maximum reactions to be of mild nature (252 out of 485 reactions) followed by moderate nature (233 out of 485 reactions). No ADR of severe nature was found out in the study.

DISCUSSION

Ovarian cancer is on the rise worldwide. It is the eighth most common cancer in women worldwide. Greatest clinical hurdle is due to rapid progression and bad prognosis of ovarian cancer, ultimately, leading to majority of deaths in patients.⁵ Limited data is available in general and in India in particular, on drug utilization in cases of ovarian cancer. We undertook this study in order to understand the pattern of drug use and adverse drug reactions in females with ovarian cancer. Majority of our patients were in the age range of 60-70 years. Patients <20 years of age were the least (four patients). In a study conducted by Zohre Momenimovahed et al, increased incidence of this cancer in women over 65 years of age was observed.¹² Another study conducted by Zheng G et al. 2018, revealed age at diagnosis to be between 50–79 years in ovarian cancer patients.¹³ The findings of our study were in consensus with both of the above mentioned studies. Most of the patients were on combination chemotherapy of Paclitaxel and Carboplatin which is supported by the previous studies conducted by G. Aravantos et al.¹⁴ Paclitaxel was commonly used antineoplastic agent as in previous study by Ozols RF et al.¹⁵ All the cases in our study were treated with Parenteral Dexamethasone [Corticosteroid], Parenteral Ranitidine [H₂-receptor antagonists], Parenteral Ondansetron / Granisetron [Serotonin 5-HT₃ receptor antagonist], Ferrous Sulphate tablets and Multivitamin B Complex tablets, as adjuvant drugs to treat the known ADRs to the given chemotherapeutic agents. Analgesics like tablet Tramadol was found to be prescribed in 32.35% of cases followed by Antipyretics like Tablet Paracetamol in 30% of the cases in our study to treat the fever and painful cancerous condition of ovarian cancer. In this study, all the drugs were prescribed by their Generic name, which is a very encouraging finding. This is possible because the institution in which the present study was done has adopted the Health Management Information System (HMIS) for drug prescribing which allows prescribing by generic names only.

Prescribing by Generic name allows flexibility of stocking and dispensing various brands of a particular drug that are cheaper than and as effective as proprietary brands. This is the basis of use of drugs from essential drug list.¹⁶ Hence, there is a need to encourage prescribing by generic names, particularly in hospitals attached to medical colleges. Some of the well documented ADRs of this drug include nausea, vomiting, tingling, numbness, alopecia, weakness, body ache and anorexia. Most of the ADRs documented in this study comprised one or more of these reactions. Although adequate pre-medication with Parenteral Dexamethasone, Ranitidine and Ondansetron/ Granisetron were given to each patient, the frequency of nausea and vomiting remained high due to high emetogenic potential of paclitaxel, carboplatin and cisplatin.¹⁷ These drugs may induce vomiting by both a central action on the chemoreceptor trigger zone (CTZ) and a peripheral action on the gastrointestinal tract. The dominant receptors in the CTZ located in the floor of the fourth ventricle are serotonin type 3 (5-HT₃) and dopamine type 2 (D₂). As serotonin receptors in the brain are involved in the mechanism of acute onset vomiting, Ondansetron has a definite role in its prevention.¹⁸ The most frequent adverse effects include Alopecia, Nausea and Vomiting. The study has demonstrated the need to improve the management of nausea and vomiting, since the rates of prevention of these expected adverse effects were poor. In this study, we observed 85.29% patients were having Alopecia as ADR in contrast to study of Boyd LR et al. where Nausea, Vomiting were the commonest observed ADRs.¹⁹ Hair loss has been rated as one of the most distressing side effect of chemotherapy, along with Nausea and Vomiting. Of 145 patients who developed Alopecia, 124 patients were on Paclitaxel, 117 patients were on Carboplatin. So hair loss seems to be more common with Carboplatin and Paclitaxel combination. Some of the rarer reactions observed were Pigmentation of tongue, lips and Oral ulcers. Pigmentation of tongue and lips was seen in 2.35% of the patients which can occur due to mucosal cell toxicity. In the squamous mucosa, there is increased pigmentation of basilar keratinocytes and an increased number of melanophages in the lamina propria of mucosa due to liposomal doxorubicin.²⁰ According to values of complete haemogram taken pre and post treatment, there were no reports of haematological disturbances like thrombocytopenia which are commonly seen with drugs like Carboplatin. In present study, most of the ADRs have been identified as 'Definite' [45.56%] by Naranjo's algorithm⁹ which is in consensus with a study conducted by Surendiran et al.²¹ Few ADRs [29.90%] seen were categorized under 'Probable' reactions in our study. Some reactions were categorized as 'Possible' [24.54%] reactions in our study.¹¹ There were no "Doubtful" drug reactions as the investigator was trained in methods of Pharmacovigilance and such complaints were avoided. Majority ADRs were preventable. In present study, majority of ADRs were 'Definitely Preventable' [63.91%] by Modified Schumock and Thornton scale which supported the study findings by Asawari L Raut et al.¹⁰ Few of ADRs [30.73%] were notified under the category of 'Not

Preventable'. Very small number of ADRs [5.36%] noted were categorized as 'Probably Preventable'. Common ADRs like nausea and vomiting can be effectively controlled. This brings out the possible toxicity that 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. So modification in the management of nausea and vomiting is needed.

Most of the reactions were of mild severity [51.96%] and there would be no strong indication to change or withhold the drug for mild adverse effects. 48.04% of reactions were moderate in nature, for which the required treatment was instilled to the respective patient. No severe level of reactions were seen in any of our patients, which needed any intensive care. This data may provide an approximate estimate of the proportion of the population treated daily with a particular drug or group of drugs²² in ovarian cancer and for various Pharmacoepidemiological studies.

CONCLUSION

Drug utilization review for anticancer drugs are essential among health care professionals as it highlights the importance of assessing optimal drug use. There is a need to strengthen the mechanism for continuing professional development of practitioners to ensure that they have the necessary knowledge and skills to prescribe rationally through continuing medical education (CME) courses on newer drug combinations, new drug molecules introduced into the market and adverse drug reactions will go a long way in curbing irrational prescribing. Drug utilization and ADR monitoring studies of this type may ultimately help in improving the quality of healthcare given to the ovarian cancer patients.

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