

## Adverse Drug Reactions Due to Cancer Chemotherapy in Females

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### ABSTRACT

In this study, occurrence of adverse drug reactions in female patients receiving chemotherapy were analyzed. Various drugs prescribed for cancer patients for compensation of these adverse reactions were also noted. Study was conducted on 83 female cancer patients selected randomly from a recent record of six months in KIRAN (Karachi Institute of Radiology and Nuclear Medicine) hospital, Karachi, Pakistan. Only those cases were selected in which patients received at least three cycles of cancer chemotherapy. The collected reports were analyzed for patients' data, drug details, causality, preventability and severity of adverse effects. Causality was assessed by the World Health Organization (WHO) causality assessment scale. Preventability and severity of ADRs were assessed by Naranjo's Algorithm and modified Hartwig's and Siegel scale. Out of n=83 females, n=55 (66.26%) females were married. Majority belonged to lower socioeconomic class (n=64, 77.10%). In the 40-49 years age group 30.12% (n=25) adverse drug reactions (ADRs) were seen whereas 26.50% (n=22) ADRs in 50-59 years of age and 25.30% (n=21) ADRs in 30-39 years of age group were observed. The cases observed were of breast cancer (n=52, 62.65%), ovarian cancer (n=14, 16.86%), GI Cancer (n=8, 9.63%), and others that include head and neck cancer (n=3, 3.61%), lymphomas (n=3, 3.61%), sarcomas (n=2, 2.40%) and mass on chest wall (n=1, 1.20%). In general, the common adverse effects observed were neutropenia/pancytopenia/anemia (n=64, 77.10%), alopecia (n=51, 61.44%), nausea and vomiting (n=39, 46.98%), fatigue/anorexia (n=26, 31.32%), mouth sores (n=21, 25.30%), fever and chills (n=20, 24.09%) and diarrhea (n=12, 14.45%). According to the three scales employed for ADRs assessment {i.e. (WHO) causality assessment scale, Naranjo's Algorithm and modified Hartwig's and Siegel scale for preventability and severity of ADRs}, the results are in close agreement with each other with respect to occurrence and severity of the ADRs. A number of ADRs are observed in various cancer patients receiving chemotherapy indicating high need of ADR monitoring and reporting. The problem of under-reporting of ADRs is a big issue and must not be overlooked.

**Keywords:** Chemotherapy, Adverse Drug Reactions, Cancer, Hartwig and Siegel Scale, WHO Causality Assessment Scale, Naranjo's Algorithm.

### INTRODUCTION

Cancer is the uncontrolled growth and spread of uncharacteristic cells. Two gene classes that may be

responsible in development of cancer are (a) Oncogenes: causing over production of proteins, stimulating cell proliferation and (b) Tumor suppressor genes: encoding for proteins, controlling improper cell division or growth<sup>[1]</sup>.

Patients are treated with different drugs at the same time in Combination chemotherapy and the principal gain is minimizing the chances of resistance due to any one

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agent. Neo-adjuvant chemotherapy is preoperative treatment designed to shrink the primary tumor rendering local therapy (surgery or radiotherapy) less disparaging or more successful [2]. The frequency and duration of chemotherapy cycles are restricted due to toxicity to the patient [3]. Since different drugs work through different cytotoxic mechanisms, they can be given jointly at full doses in chemotherapy regimens [4].

World Health Organization (WHO) defines an ADR as “any response to a drug which is harmful, inadvertent and occurs at doses used in man for prophylaxis, diagnosis or therapy” [5]. The data on ADRs has shown that it has become one of the top ten causes of death in the US yearly [6] and represents a major clinical problem for humans and healthcare costs [7]. Chemotherapeutic drugs have a narrow therapeutic index and early recognition of drug toxicity helps to amend the course of drug therapy to diminish toxic effects [8]. A recent study from a South Indian tertiary care teaching hospital has reported antineoplastic agents as common drugs class causing the ADRs [9]. Many of the adverse effects of antineoplastics are an extension of their therapeutic action disturbing all fast dividing cells [10]. ADRs are mostly not preventable due to the poor predictability and poorly understood mechanisms. However, with satisfactory pre-medication, common ADRs like nausea and vomiting can be efficiently controlled. In this connection, the patients should also be counseled well about the therapy and its effects before starting the therapy so as to manage any ADRs timely [11].

## METHODOLOGY

All patients who received the prescribed intravenous cancer chemotherapy of at least three cycles in KIRAN Hospital (Karachi Institute of Radiology and Nuclear Medicine), Karachi, Pakistan, were selected in this study. Patients who are less than 12 years of age and the out-patients were excluded from the study. The researchers selected 83 female patients' cases randomly from a recent record of six months in KIRAN Hospital. The study was conducted from March to May, 2012. Necessary patients' details were collected from the case records on a specially designed Performa with the help of doctors present on site. The ADRs based on WHO causality definitions were included in the study [12]. Severity and preventability assessments were done as per the Naranjo Algorithm [13] and modified Hartwig and Siegel scale [14]. The causality was assessed by using the World Health Organization (WHO) causality assessment scale [15].

## RESULTS

Among the cases studied, there were 83 females having different types of cancers. It was recorded from the patients' files that 77.10% (n=64) patients belonged to lower socioeconomic class; while 21.68% (n=18) belonged to middle class and 1.20% (n=1) belonged to upper class. Among 83 females, 66.26% (n=55) patients were married while 19.27% (n=16) were unmarried. The calculated average BMI of these cancer patients was 24.30 kg/m<sup>2</sup>.

### Regimens for Various Types of Cancers:

83 cases of various types of cancers were recorded from the female cancer patients' files (Fig.1). Majority patients received 3 to 6 cycles of the prescribed regimen.

| Type of cancer         | Cancer Stage  | Number of Cycles of regimen |
|------------------------|---------------|-----------------------------|
| • Breast Cancer        | Stage 3 and 4 | 10                          |
| • Ovarian Cancer       | Stage 3       | 4                           |
| • Head and Neck Cancer | Stage 2 and 4 | 7                           |
| • GI cancer            | Stage 2 and 3 | 6                           |
| • Lymphoma             | Stage 4       | 6                           |
| • Other cancers        | Stage 3       | 6                           |

Patients were given: injection Pheniramine melete, injection Dexamethasone, injection Metoclopramide, injection Ranitidine, tablet Prednisolone and Normal Saline or Ringer's Lactate as premedications for different expected symptoms as per requirement of the patient and these are in line with the standard treatment.

Among 52 (62.65 %) women with breast cancer, 34 (40.96%) were treated with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) with or without paclitaxel, doxetaxel and vinorelbine. Fourteen (16.86%) women were treated with AC (doxorubicin and cyclophosphamide) with or without paclitaxel and doxetaxel.

Out of 8 (9.63%) patients of GI Cancer, two (2.40%) patients of colorectal carcinoma received FOLFOX regimen (5-fluorouracil, folinic acid and oxaliplatin) whereas 3 (3.61%) patients received FL (5-fluorouracil and folinic acid). Two (2.40%) patients of oesophageal cancer were on cisplatin with 5-fluorouracil and one patient (1.20%) with gall bladder cancer was treated with carboplatin plus gemcitabine.

In total 3 (3.61%) patients with Hodgkin's and non Hodgkin's lymphoma (stage IV), one (1.20%) patient received ABVD therapy (doxorubicin, bleomycin,

vinblastine, and dacarbazine); two (2.40%) were on CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone which is the standard of care for patients with diffuse large-B-cell lymphoma.

There were 3 (3.61%) cases of head and neck cancer out of which 2 (2.40%) patients were on cisplatin with 5-fluorouracil and one (1.20%) patient was on cisplatin, 5-fluorouracil and carboplatin regimen.

In 14 (16.86%) cases of ovarian cancer, 10 (12.04%) patients were receiving paclitaxel with carboplatin and 4 (4.81%) were on BEP (bleomycin, etoposide, and cisplatin) chemotherapeutic regimen.

Two (2.40%) patients of sarcomas were observed in which one (1.20%) case of Ewing's sarcoma was receiving VAC-IE therapy (vincristine, actinomycin, cyclophosphamide- ifosfamide and etoposide) and one (1.20%) case of rhabdo-myosarcoma was on VAC therapy (vincristine, actinomycin, cyclophosphamide).

**Adverse Drug Reactions:**

Fig. 2 shows that ADRs mostly occurred in the age group of 40-49 years (n=25, 30.12%). It is evident from the estimation of ADRs that most of the patients (n=64, 77.10%) had risk for developing neutropenia/ anemia/ pancytopenia, alopecia (n=51, 61.44%) and nausea and

vomiting (n=39, 46.98%) (Table 1); mucositis was in 25.3% (n=21) and 31.32% (n=26) patients suffered from fatigue and tiredness during chemotherapy. It can be seen that patients suffered from more than one ADR at a time (Table 1).

The drugs used for management of ADRs in the observed cases were:

- Metoclopramide and Dimenhydrinate for nausea and vomiting.
- Filgrastim, Blood transfusion, vitamin B 12, Iron complex and Ceftazidime in myelosuppression.
- Mouth wash and Nystatin drops for mouth sores; Fluconazole in mucositis.
- Loperamide Hydrochloride and Dicotahedral smectite for diarrhea.
- Normal Saline and Ringer's Lactate for electrolyte imbalance.
- Prednisolone and Dexamethasone preparations in skin changes.
- Aluminium hydroxide, Magnesium hydroxide, Oxethazaine, Ranitidine and Omeprazole in hyperacidity, ulcers and dyspepsia.
- Acetaminophen, Mefenamic acid and Diclofenac sodium for pain management.
- Furosemide to relieve edema.
- Alprazolam in anxiety.
- Cyproheptadine and Multivitamins in anorexia.
- Pholcodine, Pseudoephedrine HCl, Chlorpheniramine maleate and menthol syrup for cough.

#### ADR Assessment Using Various Scales:

From the Naranjo Algorithm Scale <sup>[13]</sup>, it was observed that 59 (71.08 %) cases of Neutropenia/Anemia/Pancytopenia and 25 (30.12%) cases of alopecia were 'Definite'; 23 (27.71%) cases of alopecia and 17 (20.48%) cases of nausea/vomiting were 'probable'; there were 12 (14.45%) cases of 'Possible' nausea/vomiting; 3 (3.61%) cases of dyspnoea/ shortness of breath were 'Doubtful' (Table 2). Hence, all the ADR results depend on various types/cycles of chemotherapies employed.

The Modified Hartwig and Siegel Severity Assessment <sup>[14]</sup> showed 51 (61.44 %) cases of Alopecia,

20 (24.09%) cases of fatigue/tiredness/anorexia and 20 (24.09%) cases of neutropenia/anemia/pancytopenia to be 'Mild'; 27 (32.53%) cases of Nausea/Vomiting and 15 (18.07%) cases of mouth sores/ulcers to be 'Moderate', 44 (53.01%) cases of neutropenia/Anemia/pancytopenia to be 'severe' and none to be 'Lethal' (Table 2).

The WHO Causality Assessment <sup>[15]</sup> revealed 64 (77.10%) cases of neutropenia/anemia/pancytopenia, 51 (61.44%) cases of alopecia and 39 (46.98%) cases to be 'Certain'; 15 (18.07%) cases of fever/chills, 11 (13.25%) cases of skin changes and 10 (12.04%) cases of dyspepsia to be 'likely/probable'; 5 (6.02%) cases of headache/pain and 4 (4.81%) cases of cough and electrolyte imbalance to be 'unlikely' (Table 2).

Table (3) shows that various regimens are related to the occurrence of various ADRs which cause distress and anxiety among cancer patients. The most common regimens which were observed associated with various major ADRs were AC + Taxol (alopecia, neutropenia/ anemia/ pancytopenia), FAC + combinations (neutropenia/ anemia/ pancytopenia), 5 FU + Cisplatin nausea/ vomiting, alopecia, neutropenia/ anemia/ pancytopenia, mouth sores/ ulcers), BEC (nausea/ vomiting), FL (alopecia, diahorrea/ constipation) and Carboplatin + Taxol (neutropenia/anemia/pancytopenia) regimens (Table 3).

#### DISCUSSION

Various chemotherapeutic agents may be used in combination for treating breast cancer depending on factors such as tumor characteristics, lymph node status, and the age and health of the patient <sup>[16]</sup>. Use of AC regimen followed by taxol regimen for cost effectiveness of therapy was observed in case of women belonging to lower socio-economic class. In this study, majority women (n=34, 40.96%) were treated with FAC therapy with or without paclitaxel, doxetaxel and vinorelbine.

The standard adjuvant treatment of colon cancer is fluorouracil plus leucovorin (FL). It is reported that Oxaliplatin improves the effectiveness of this combination in the patients with metastatic colorectal cancer <sup>[17-21]</sup>. In this study, fluorouracil combinations were

used for the treatment of GI cancers. Among the 3 (3.61%) lymphoma patients observed, 2 were receiving CHOP regimen which is the standard treatment for young and elderly patients [22]. For advanced Hodgkin's disease, MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimens are reported as standard chemotherapeutic combinations [23-24]. Out of 3 (3.61%) cases, 2 cases of head and neck cancer were treated with the most common combination of cisplatin and 5-fluorouracil [25] and majority of patients with ovarian cancer (n=10, 12.04%) were given paclitaxel with carboplatin. Many oncologists favor using carboplatin over cisplatin, due to the results found in a recent phase III trial conducted by the Gynecologic Oncology Group (GOG-158) [26].

The reasons for the amplified occurrence of ADRs in females may be due to the different factors like puberty, pregnancy, life style, environment, etc [8, 27, 28]. The ADRs were observed mostly in patients between 40-49 years of age (n=25, 30%) which may be due to the stumpy metabolizing capacity and reduced excretory functions [8, 9, 28]. Mostly (n=64, 21.12%) patients suffered from neutropenia/ anemia/ pancytopenia due to myelosuppression during chemotherapy and this may be life threatening [8] (Table 1). Alopecia (n=51, 61.44%) was also a frequent and inescapable ADR found during cancer chemotherapy [29]. From the assessment of various scales employed for ADRs estimation, it was also observed that most common ADRs experienced by the patients were neutropenia/anemia/pancytopenia [8] and alopecia [29]. It is notorious that nausea and vomiting develop after chemotherapy treatment which depends on several factors e.g. sex and age in female patients; younger patients are at greater risk [30-32]. In the study, it was observed that (n=39, 46.98%) patients developed

nausea and vomiting after chemotherapy. The antiemetic agents are helpful in decreasing the occurrence of nausea and vomiting and benzodiazepines can be taken orally prior to chemotherapy treatment to reduce anticipatory nausea [30, 33-34]. According to several studies, fatigue affects up to 70% of patients during chemotherapy and radiotherapy [35-36] and limits normal daily activities; 31.32% (n=26) patients were observed with fatigue and tiredness during chemotherapy. Up to 30% of cancer survivors experienced fatigue for years even after stopping the treatment. [37-38]. Some cancer patients who participated in an aerobic training program experienced a reduction in fatigue [39-40]. Diarrhea may come about due to mucosal cell toxicity and mucosal tissue injury is a dose-limiting consequence which causes weight loss and nutritional deficits for many patients [41-42]; this was observed in n=12 (14.45%) patients in the study. It can also be seen in Table (3) that alopecia [29], nausea/vomiting [30-32], neutropenia/anemia/pancytopenia [8] and fatigue/tiredness [35-36] are the common ADRs encountered due to the use of various chemotherapeutic agents employed.

ADRs are not preventable but their incidence can be decreased by timely use of various medications. Patients' tolerance is an important factor and there is a high need for patient counseling about the therapy and possible ADRs during treatment.

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Table 1. Overall Types of ADRs Observed

| ADRs OBSERVED PER PATIENT           | IN NO. OF CYCLES (CHEMOTHERAPY)= | NO. OF PATIENTS HAVING ADRs (OUT OF 83) | PATIENTS (%) HAVING ADRs |
|-------------------------------------|----------------------------------|---|--------------------------|
| NAUSEA, VOMITING                    | C1-C10                           | 39                                      | 46.98                    |
| FATIGUE/TIREDNESS/ANOREXIA          | C1-C7                            | 26                                      | 31.32                    |
| ALOPECIA                            | C3-C7                            | 51                                      | 61.44                    |
| NEUTROPENIA/ANEMIA/PAN<br>CYTOPENIA | C1-C10                           | 64                                      | 77.10                    |
| BLEEDING                            | C4-C7                            | 4                                       | 4.81                     |
| MOUTH SORES/ULCERS                  | C3-C7                            | 21                                      | 25.30                    |
| DIARRHOEA/CONSTIPATION              | C2-C10                           | 12                                      | 14.45                    |
| FEVER/CHILLS                        | C3-C7                            | 20                                      | 24.09                    |
| HEADACHE/PAIN                       | C4-C7                            | 5                                       | 6.02                     |
| ITCHING/SWELLING                    | C4-C7                            | 10                                      | 12.04                    |
| EDEMA                               | C3-C6                            | 4                                       | 4.81                     |
| SKIN CHANGES                        | C3-C9                            | 11                                      | 13.25                    |
| DYSPEPSIA                           | C3-C7                            | 10                                      | 12.04                    |
| EPIGASTRIC PAIN                     | C3-C4                            | 2                                       | 2.40                     |
| DYSPNEA/SOB                         | C3-C4                            | 3                                       | 3.61                     |
| DEAFNESS/ EAR CLOSED                | C4                               | 1                                       | 1.20                     |
| DYSURIA                             | C3                               | 1                                       | 1.20                     |
| INSOMNIA/ANXIETY                    | C2                               | 1                                       | 1.20                     |
| NEUROPATHY                          | C4                               | 1                                       | 1.20                     |
| COUGH                               | C4                               | 4                                       | 4.81                     |
| ALLERGY                             | C2                               | 1                                       | 1.20                     |
| DYSPHASIA                           | C6                               | 1                                       | 1.20                     |
| INFECTION                           | C3-C7                            | 6                                       | 7.22                     |
| FOLIC ACID DEFICIENCY               | C3                               | 1                                       | 1.20                     |
| ELECTROLYTE IMBALANCE               | C3                               | 4                                       | 4.81                     |

Table 2. Various Scales Used For ADRs Assessment

| SCALES USED FOR ADRs ASSESSMENT            |                     |          |           |                          |           |          |                   |           |          |           |
|--|---------------------|----------|-----------|--------------------------|-----------|----------|-------------------|-----------|----------|-----------|
| ADVERSE DRUG REACTIONS (ADR <sub>s</sub> ) | WHO CAUSALITY SCALE |          |           | HARTWIG AND SIEGEL SCALE |           |          | NARANJO ALGORITHM |           |          |           |
|  | <i>C</i>            | <i>L</i> | <i>UL</i> | <i>MI</i>                | <i>MO</i> | <i>S</i> | <i>DE</i>         | <i>PR</i> | <i>P</i> | <i>DO</i> |
| NAUSEA, VOMITING                           | 39                  | 0        | 0         | 12                       | 27        | 0        | 10                | 17        | 12       | 0         |
| FATIGUE/TIREDNESS/ANOREXIA                 | 22                  | 4        | 0         | 20                       | 6         | 0        | 15                | 11        | 0        | 0         |
| ALOPECIA                                   | 51                  | 0        | 0         | 51                       | 0         | 0        | 25                | 23        | 3        | 0         |
| NEUTRO/ANEMIA/PANCYTOPENIA                 | 64                  | 0        | 0         | 20                       | 0         | 44       | 59                | 5         | 0        | 0         |
| BLEEDING                                   | 0                   | 3        | 1         | 1                        | 3         | 0        | 0                 | 0         | 4        | 0         |
| MOUTH SORES/ULCERS                         | 21                  | 0        | 0         | 5                        | 15        | 1        | 10                | 9         | 2        | 0         |
| DIARRHOEA/CONSTIPATION                     | 12                  | 0        | 0         | 2                        | 10        | 0        | 5                 | 3         | 4        | 0         |
| FEVER/CHILLS                               | 5                   | 15       | 0         | 7                        | 13        | 0        | 11                | 9         | 0        | 0         |
| HEADACHE/PAIN                              | 0                   | 0        | 5         | 3                        | 2         | 0        | 4                 | 1         | 0        | 0         |
| ITCHING/SWELLING                           | 8                   | 2        | 0         | 10                       | 0         | 0        | 0                 | 4         | 6        | 0         |
| EDEMA                                      | 0                   | 4        | 0         | 3                        | 1         | 0        | 4                 | 0         | 0        | 0         |
| SKIN CHANGES                               | 0                   | 11       | 0         | 2                        | 9         | 0        | 7                 | 0         | 4        | 0         |
| DYSPEPSIA                                  | 0                   | 10       | 0         | 0                        | 10        | 0        | 2                 | 6         | 1        | 1         |
| EPIGASTRIC PAIN                            | 0                   | 2        | 0         | 0                        | 2         | 0        | 0                 | 1         | 0        | 1         |
| DYSPNEA/SOB                                | 0                   | 0        | 3         | 3                        | 0         | 0        | 0                 | 0         | 0        | 3         |
| DEAFNESS/ EAR CLOSED                       | 0                   | 0        | 1         | 1                        | 0         | 0        | 0                 | 0         | 0        | 1         |
| DYSURIA                                    | 0                   | 0        | 1         | 1                        | 0         | 0        | 0                 | 0         | 0        | 1         |
| INSOMNIA/ANXIETY                           | 0                   | 0        | 1         | 1                        | 0         | 0        | 0                 | 0         | 1        | 0         |
| NEUROPATHY                                 | 0                   | 0        | 1         | 1                        | 0         | 0        | 0                 | 1         | 0        | 0         |
| COUGH                                      | 0                   | 0        | 4         | 0                        | 4         | 0        | 0                 | 0         | 4        | 0         |
| ALLERGY                                    | 0                   | 1        | 0         | 0                        | 1         | 0        | 0                 | 0         | 1        | 0         |
| DYSPHASIA                                  | 0                   | 0        | 1         | 1                        | 0         | 0        | 0                 | 0         | 0        | 1         |
| INFECTION                                  | 0                   | 6        | 0         | 0                        | 6         | 0        | 6                 | 0         | 0        | 0         |
| FOLIC ACID DEFICIENCY                      | 0                   | 0        | 1         | 1                        | 0         | 0        | 0                 | 0         | 0        | 1         |
| ELECTROLYTE IMBALANCE                      | 0                   | 4        | 0         | 4                        | 0         | 0        | 4                 | 0         | 0        | 0         |

**Where:**

C= certain, L= likely, UL= unlikely

MI= mild, MO= moderate, S= severe

DE= definite, PR= probable, P= possible, DO= doubtful

Table 3. ADRs Due to Various Treatments/Regimens

| ADVERSE DRUG REACTIONS (ADRs)     | DIFFERENT TREATMENTS/REGIMEN |      |     |        |    |     |         |     |                 |          |                   |                   |                     |
|-----------------------------------|------------------------------|------|-----|--------|----|-----|---------|-----|-----------------|----------|-------------------|-------------------|---------------------|
|                                   | CHOP                         | ABVD | FAC | FOLFOX | FL | BEC | 5FU+Cis | Cis | FAC+OTHER DRUGS | AC+TAXOL | CARBOPLATIN+TAXOL | TAXOL+OTHER DRUGS | LESS COMMON REGIMEN |
| NAUSEA/VOMITING                   | 2                            | -    | 1   | 2      | 3  | 5   | 6       | 1   | 1               | 2        | 5                 | 2                 | 3                   |
| FATIGUE/TIREDNESS/ANOREXIA        | -                            | -    | 1   | 1      | -  | -   | 3       | -   | 1               | 5        | -                 | -                 | 3                   |
| ALOPECIA                          | 1                            | -    | 4   | -      | 4  | -   | 4       | 2   | 2               | 10       | 1                 | 2                 | 6                   |
| NEUTROPENIA/ANEMIA / PANCYTOPENIA | 2                            | -    | 3   | 1      | 2  | 3   | 4       | -   | 5               | 11       | 8                 | 2                 | 4                   |
| BLEEDING                          | -                            | -    | -   | -      | -  | 1   | 1       | -   | -               | -        | -                 | -                 | -                   |
| MOUTH SORES/ULCERS                | -                            | -    | 1   | 1      | 3  | 1   | 4       | 1   | 1               | 2        | 1                 | -                 | 2                   |
| DIARRHOEA/CONSTIPATION            | 1                            | -    | -   | 1      | 4  | 3   | 1       | -   | -               | -        | -                 | 1                 | 4                   |
| FEVER/ CHILLS                     | 1                            | -    | 2   | 1      | -  | -   | 2       | -   | 2               | 1        | -                 | -                 | 3                   |
| HEADACHE/ PAIN                    | -                            | -    | 1   | 2      | 1  | 1   | 3       | -   | 3               | 1        | -                 | -                 | -                   |
| ITCHING/SWELLING                  | -                            | -    | -   | 1      | -  | -   | 2       | 6   | 1               | 2        | -                 | -                 | -                   |
| EDEMA                             | -                            | -    | -   | -      | -  | -   | 1       | -   | -               | -        | -                 | -                 | -                   |
| SKIN CHANGES                      | -                            | -    | -   | -      | 1  | -   | 3       | -   | 1               | 1        | -                 | -                 | 2                   |
| OTHER TOXICITIES                  | 1                            | -    | 4   | 1      | -  | 1   | 5       | -   | 3               | 7        | 1                 | 2                 | 2                   |

**Where:**

CHOP= Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

ABVD= Doxorubicin, Bleomycin, Vinblastine, Dacarbazine

FAC= 5-Fluorouracil, Adriamycin(Doxorubicin), Cyclophosphamide

FL= 5-Fluorouracil, Folinic acid

FOLFOX= 5-Fluorouracil, Oxaliplatin, Folinic acid (leucovorin),

BEC= Bleomycin, Etoposide, Cisplatin

AC= Adriamycin, Cyclophosphamide

Cis= Cisplatin

**NOTE:** The less common treatments/regimens include Docetaxel or Paclitaxel with Trastuzumab; VAC-IE (vincristine-actinomycin-cyclophosphamide-ifosfamide-etoposide) with Mesna; CVP (cyclophosphamide-vincristine-prednisone); VAC (vincristine-actinomycin-cyclophosphamide).

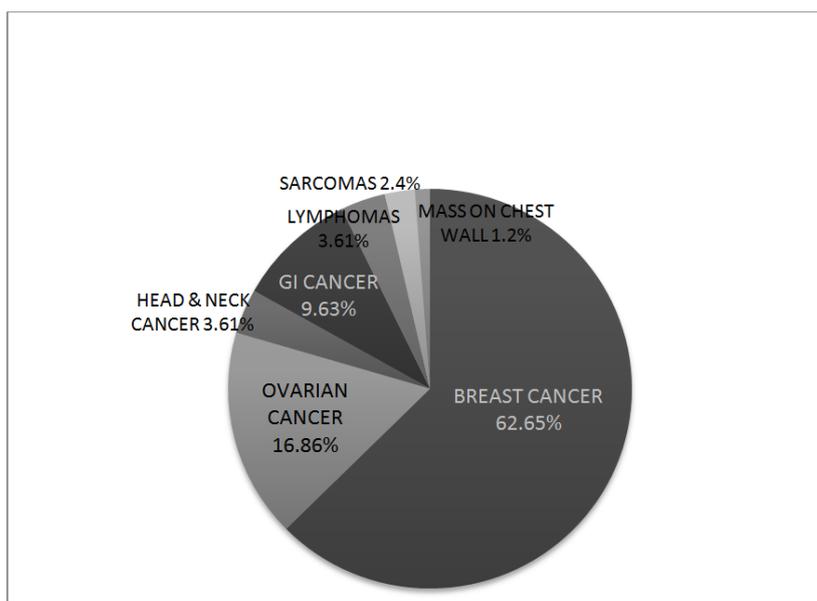


Fig 1. Percentage of Cancer Prevalence

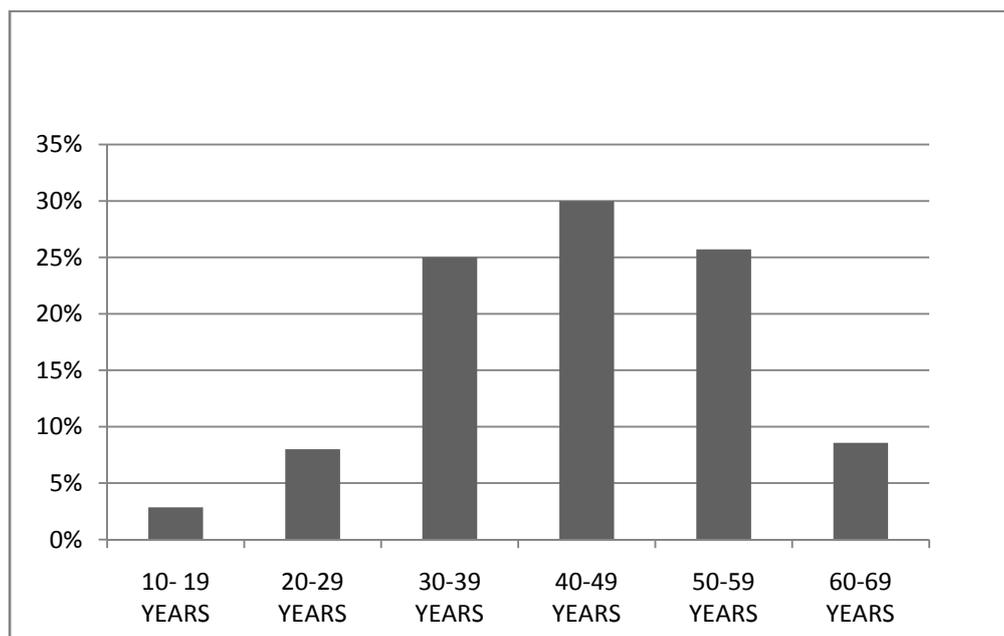


Fig. 2. Occurrence of ADRs in Various Age Groups

## REFERENCES

- (1) Mark Kirstein. Neoplastic Disorders and their treatment: General Principles, Section 19, Chapter 88-2. In: Applied Therapeutics; *The Clinical Use of Drugs*, 9<sup>th</sup> Ed. Lippincott Williams and Wilkins. 2009
- (2) Skeel, R. T. Handbook of Cancer Chemotherapy. 2007; 7<sup>th</sup> ed. p. 34,36 Lippincott Williams & Wilkins.
- (3) Chabner, B.; Longo, D. L. Cancer Chemotherapy and Biotherapy: *Principles and Practice*. 2005; 4<sup>th</sup> Ed. Philadelphia: Lippincott Williams & Wilkins.
- (4) Mayer, R. J. Targeted therapy for advanced colorectal cancer -- more is not always better. *N. Engl. J. Med.* 2009; 360:623
- (5) Lazarou J, Pomeranz B.H and Corey P.N. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *J. Am. Med. Assoc.*, 1998; 279(15): 1200-1205.
- (6) Lee, A., and Thomas, S.H.L. Adverse drug reactions. In: Clinical Pharmacy and Therapeutics (Roger Walker and Clive, Editors) 2003; 3<sup>rd</sup> ed. p. 33-34. Spain: Churchill Livingstone.
- (7) Nerurkar R.P, Nadkar M.Y, Bichile S.K. Need for monitoring adverse drug reactions. *J Assoc Physicians India* 1998; 46:673-4. [PubMed]
- (8) Sneegda Poddar, Razia Sultana. Pattern of Adverse Drug Reactions Due to Cancer Chemotherapy in Tertiary Care Teaching Hospital in Bangladesh. Dhaka Univ. *J. Pharm. Sci.* 2009; 8(1): 11-16.
- (9) Jose, J. and Rao, P.G. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. *Pharmacol. Res.* 2006; 54, 226-233.
- (10) Sweetman, S.C. In: Martindale: The Complete Drug Reference London Pharmaceutical Press. 2002; 33<sup>rd</sup> ed. p.645.
- (11) Surendiran A, Balamurugan N, Gunaseelan K, Akhtar S, Reddy KS, Adithan C. Adverse drug reaction profile of cisplatin-based chemotherapy regimen in a tertiary care hospital in India: An evaluative study. *Indian J Pharmacol.* 2010; 42(1): 40-43 [PubMed]
- (12) Edwards, I.R. and Aronson, J.K. Adverse drug reactions: Definitions, diagnosis and management. *Lancet.* 2000; 356:1255-1259.
- (13) Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt D.J. A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.* 1981; 30:239-245.
- (14) Hartwig S.C, Siegel J. and Schneider P.J. Preventability and severity assessment in reporting adverse drug reactions. *Am. J. Hosp. Pharm.*, 1992; 49: 2229-2232.
- (15) The use of the WHO-UMC system for standardised case causality assessment <http://who-umc.org/Graphics/24734.pdf>
- (16) Von Minckwitz, G. Docetaxel/anthracycline combinations for breast cancer treatment. Expert Opinion on Pharmacotherapy. 2007; 8:485-495.
- (17) Thierry André, M.D., Corrado Boni, M.D., Lamia Mounedji-Boudiaf, M.D. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. The New England journal of medicine. *N. Engl. J. Med.* 2004; 350:2343-51.
- (18) Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil leucovorin as first-line treatment of metastatic colorectal cancer. *J. Clin. Oncol.* 2000; 18:136-47.
- (19) De Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J. A, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, and Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J. Clin. Oncol.* 2000; 18:2938-47.
- (20) Goldberg R.M, Sargent D.J, Morton R.F, Fuchs C. S. Ramanathan R. K, Williamson S.K., Findlay B. P, Pitot H.C, and Alberts S.R. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J. Clin. Oncol.* 2004; 22:23-30.
- (21) Fisher R.I, Gaynor E.R, Dahlberg S, Oken M. M, Grogan T. M, Mize E. M, Glick J. H, Coltman C. A Jr., and Miller T.P. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N. Engl. J. Med.* 1993; 328:1002-6.
- (22) Connors J.M, Klimo P, Adams G, Burns B. F, Cooper I,

- Meyer R. M, O'Reilly S. E, Pater J, Quirt I, Sadura A, Shustik C, Skillings J, Sutcliffe S, Verma S, Yoshida S and Zee B. Treatment of advanced Hodgkin's disease with chemotherapy — comparison of MOPP/ABV hybrid regimen with alternating courses of MOPP and ABVD: a report from the National Cancer Institute of Canada clinical trials group. *J. Clin. Oncol.* 1997; 15:1638-45.
- (23) Cullen M.H, Stuart N.S, Woodroffe C, Murphy A, Fletcher J, Blackledge G. R, Child J. A, Grieve R. J and Jones E. L. VPP/PAB10E and radiotherapy in advanced stage Hodgkin's disease. *J. Clin. Oncol.* 1994; 12:779-87.
- (24) Song, J. Zhong, D.-X. Qian, W. Hou, X.-H. Chen, J. D. Z. Short pulse gastric electrical stimulation for cisplatin-induced emesis in dogs. *Neurogastroenterology & Motility.* 2011; 23:468-e178.
- (25) Ozols R.F, Bundy B.N, Fowler J, Clarke-Pearson D, Mannel R, Hartenbach E.M, et al. Randomized phase III study of cisplatin(CIS)/paclitaxel (PAC) versus carboplatin (CARBO)/PAC in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial (GOG 158). *Proc Am. Soc. Clin. Oncol.* 1999;18:356a
- (26) Blacker, K., Stern, R., and Wintroub, B. U. Cutaneous reactions to drugs. *Dermatology in general medicine.* Mc Graw Hill: New York. 1993; p 1783-1794.
- (27) Wilson, K. Sex-related difference in drug disposition. *Clinical Pharmacokinetics.* 1984; 9:189-202.
- (28) Barbara G. Wells, Joseph T. Dipiro, Terry L. SCHWINGHAMMER, Cecily V. Dipiro. Breast cancer. *In: Pharmacotherapy Hand book.* Boston: McGraw-Hill: New York. 2009; 7<sup>th</sup> ed. Chapter 61, p. 679.
- (29) Bates, D.W. and Leape, L. Adverse Drug Reaction. In: Morrell's Clinical Pharmacology. Boston: McGraw-Hill. 2002, p.1223-1257..
- (30) Jordan K, Sippel C, Schmoll H.J. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: Past, present, and future recommendations. *Oncologist.* 2007; 12:1143–50. [PubMed: 17914084]
- (31) Flake Z.A, Scalley R.D, Bailey A.G. Practical selection of antiemetics. *Am. Fam. Physician.* 2004; 69:1169–74. [PubMed: 15023018]
- (32) Kiebert G.M, Hanneke J, de Haes C.J, Kievit J, van de Velde C.J. Effect of peri-operative chemotherapy on the quality of life of patients with early breast cancer. *Eur. J. Cancer.* 1990; 26(10):1038–1042.
- (33) Roscoe JA, Bushunnow P, Morrow GR, et al. Patient experience is a strong predictor of severe nausea after chemotherapy: a University of Rochester Community Clinical Oncology Program study of patients with breast carcinoma. *Cancer.* 2004; 101:2701-8
- (34) Paul J. Hesketh, M.D. Chemotherapy-Induced Nausea and Vomiting. *N. Engl. J. Med.* 2008; 358:2482-2494
- (35) Smets EMA, Garssen B, Schuster-Uitterhoeve ALJ, de Haes JCJM. Fatigue in cancer patients. *Br. J. Cancer* 1993; 68:220–4.
- (36) Devlen J, Maguire P, Phillips P, Crowther D, Chambers H. Psychological problems associated with diagnosis and treatment of lymphomas. 1. Retrospective. 2. Prospective. *BMJ.* 1987; 295:953–7.
- (37) Irvine DM, Vincent L, Bubela N, Thompson L, Graydon J. A critical appraisal of the research literature investigating fatigue in the individual with cancer. *Cancer Nurs.* 1991; 14(4): 188–99.
- (38) Berglund G, Bolund C, Fornander T, Rutqvist L.E, Sjoden P.O. Late effects of adjuvant chemotherapy and postoperative radiotherapy on quality of life among breast cancer patients. *Eur. J. Cancer* 1991; 27:1075–81.
- (39) Dimeo F.C, Tilmann M.H, Bertz H, Kanz L, Mertelsmann R, Keul J. *Aerobic exercise in the rehabilitation of cancer patients after high-dose chemotherapy and autologous peripheral stem cell transplantation.* *Cancer* 1997; 79; 9: 1117–22.
- (40) Dimeo F, Rumberger B, Keul J. Aerobic exercise as therapy for cancer fatigue. *Med. Sci. Sport Exerc.* 1998; 30:475–8.
- (41) Debra J Harris. Cancer Treatment-Induced Mucositis Pain: Strategies for Assessment and Management. *Ther. Clin. Risk Manag.* 2006; 2: 251–258.
- (42) Epstein J.B, Schubert M.M. Oral mucositis in myelosuppressive cancer therapy. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 1999; 88:273–6. [PubMed]

## تحليل حدوث التفاعلات الدوائية الضارة في المرضى الذين يتلقون العلاج الكيميائي من السرطان من الإناث

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## ملخص

في هذه الدراسة ، تم تحليل حدوث التفاعلات الدوائية الضارة في المرضى الذين يتلقون العلاج الكيميائي من الإناث، وقد لوحظ ان هناك العديد من الأدوية الموصوفة لمريضات السرطان لعلاج هذه التفاعلات الدوائية الضارة . أجريت الدراسة على 83 مريضة بالسرطان تم اختيارهن عشوائيا من سجل المرضى خلال ستة أشهر في مستشفى KIRAN (معهد كراتشي للأشعة و الطب النووي، كراتشي ، باكستان). وقد تم اختيار الحالات التي تلقت المريضات فيها ما لا يقل عن ثلاث دورات من العلاج الكيميائي للسرطان . وتم تحليل التقارير التي تم جمعها من المريضات في ما يتعلق بتفاصيل الادوية المستخدمة و التفاعلات الدوائية الضارة واسبابها وطرق اتقائها وشدة هذه الآثار السلبية. تم تقييم العلاقة السببية للتفاعلات الدوائية الضارة باستخدام نطاق العلاقة السببية الصادر من منظمة الصحة العالمية و تقييمها (WHO) . وتم تقييم طرق اتقاء التفاعلات وشدتها بواسطة خوارزمية نارانجو (Naranjo's Algorithm) ومقياس هارتفيغ و سيجل المعدل ( Hartwig's and Siegel scale). وتبين ان 55 من المريضات ( 66,26 % ) من اصل 83 مريضة، كنّ متزوجات . تنتمي غالبية المريضات للطبقة الاجتماعية والاقتصادية المنخفضة (ن = 64 ، 77,10 %). وفي الفئة العمرية 40-49 سنة، كان هناك 30,12 % (ن = 25) من التفاعلات الدوائية الضارة التي تم توثيقها، بينما كان هناك 26,50 % (ن = 22) من تلك التفاعلات في الفئة العمرية 50-59 سنة و 25,30 % (ن = 21) من تلك التفاعلات في الفئة العمرية 30-39 . وكانت الحالات التي لوحظت كما يأتي: سرطان الثدي (ن = 52)، سرطان المبيض (ن = 14)، سرطان الجهاز الهضمي (ن = 8)، وغيرها التي تشمل سرطان الرأس و الرقبة (ن = 3) ، ورم الغدد اللمفاوية (ن = 3) ، الأورام اللحمية (ن = 2) والكتلة على جدار الصدر (ن = 1) . بشكل عام ، كانت الآثار السلبية كما يأتي: انخفاض عدد كريات الدم البيضاء (neutropenia/pancytopenia) وفقر الدم (ن = 64 ، 77,10 % ) ، وفقدان الشعر (ن = 51 ، 61,44 % ) ، والغثيان والقيء (ن = 39 ، 46,98 % ) ، والتعب/ فقدان الشهية (ن = 26 ، 31,32 % ) ، وتقرحات الفم (ن = 21 ، 25,30 % ) ، وحمى و تشعيرية (ن = 20 ، 24,09 % ) ، والإسهال (ن = 12 ، 14,45 % ) . وفقا للجداول الثلاثة المستخدمة لتقييم التفاعلات؛ أي منظمة الصحة العالمية ، خوارزمية نارانجو ومقياس هارتفيغ و سيجل المعدل، فإن النتائج هي في اتفاق وثيق مع بعضها بعضا في ما يتعلق بحدوث هذه التفاعلات و شدتها . يلحظ حدوث التفاعلات الدوائية الضارة في مختلف مرضى السرطان الذين يتلقون العلاج الكيميائي مينا حاجة عالية للرصد والإبلاغ عن هذه التفاعلات الدوائية الضارة ، ومشكلة ضعف هذه التقارير هي قضية كبيرة و يجب عدم التغاضي عنها.

**الكلمات الدالة:** العلاج الكيميائي ، التفاعلات الدوائية الضارة ، السرطان، مقياس هارتفيغ و سيجل المعدل ، مقياس تقييم منظمة الصحة العالمية السببية ، خوارزمية نارانجو ل.

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