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INCIDENCE AND CHARACTERIZATION OF ADVERSE DRUG REACIONS IN PATIENTS RECEVING CHEMOTHERAPY FOR BREAST CANCER

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Abstract: **Breast cancer is ranked number one cancer among Indian females. Primary choice of treatment for cancer is chemotherapy and it is associated with toxic effects. Incidence and magnitude of adverse drug reactions (ADRs) in patients will differ accordingly. Characterizing ADRs can help in optimizing the treatment regimen.**

Methods: Patients enrolled according to inclusion criteria. Assessed for incidence of ADRs and characterized the ADRs by using Naranjo Adverse Drug Reaction Probability Scale questionnaire, WHO-UMC causality assessment system questionnaire, ADR Severity Assessment Scale (Modified Hartwig and Siegel) questionnaire and ADR Preventability Assessment Scale (Modified Schumock and Thornton) questionnaire.

Result: A total of 96 patients were enrolled in the study. The most common ADR caused by Herceptin, Docetaxel, cyclophosphamide, 5- fluorouracil were Anorexia and the second most common ADR was discoloration of nail. Allergic reactions, pancytopenia and weakness were major in Epirubicin, carboplatin, Adriamycin, Paclitaxel and Gemcitabine. Majority of the ADRs were preventable, mild and possible.

Keywords: **Adverse drug reactions, Chemotherapy.**

1. INTRODUCTION

Breast cancer is ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. The age adjusted incidence rate of carcinoma of the breast was found as high as 34.4 per 100,000 women in Bangalore. Mortality to incidence ratio was found to be as high as 66 in rural registries and as low as 8 in urban registries. Young age has been found to be a major risk factor breast cancer in Indian women. Breast cancer projection for India during time period 2020 suggests the number to go high as 1797900.[1]Primary systemic treatment for breast cancer was adjuvant chemotherapy and now it is considered as neoadjuvant chemotherapy The concomitant risks associated with cancer chemotherapy are potential adverse drug reactions (ADR), Development of secondary cancer, mental distress, worsening of Quality of life (QoL) and economic loss. The World Health Organization (WHO) defines an ADR as "any response to a drug, which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy".[2]There are substantial short- and long-term side effects from chemotherapy. By convention, short-term side effects include those toxic effects encountered during chemotherapy, while long-term side

effects include later complications of treatment arising after the conclusion of adjuvant chemotherapy. These side effects vary, depending on the specific agents used in the adjuvant regimen as well as on the dose used and the duration of treatment. There is also considerable variability in side effect profile across individuals.[3] Despite this grim picture, it is very much possible to prevent these ADRs and to treat them adequately with approaches such as dose reduction, use of alternate drugs, growth factors, and cytoprotective agents. Several strategies such as the use antiemetics, mannitol, and antiallergic drugs along with anticancer drug infusion have been in place for many years. Careful and appropriate usage of these practices remarkably reduces the burden of anticancer ADRs. Therefore, it is of vital importance to know how much and how well these strategies are employed in hospital settings and to find out the remaining lacunae and ways to manage them for all-inclusive patient management.

2. AIM

To assess the incidence and characterization of adverse drug reactions in patients receiving chemotherapy for breast cancer

3. STUDY TOOLS

The following tools will be employed to obtained information pertaining to the study:

1. **Naranjo Adverse Drug Reaction Probability Scale questionnaire** – Designed by Naranjo *et al* for determine the likelihood of whether an ADR is actually due to the drug rather than the result of other factors.

2. **WHO-UMC causality assessment system questionnaire** – Used to classify the cause of ADR into certain, probable, possible, Unlikely and un-assessable.

3. **ADR Severity Assessment Scale (Modified Hartwig and Siegel) questionnaire** – Describing the intensity of ADR as in grading mild, moderate and severe.

4. **ADR Preventability Assessment Scale (Modified Schumock and Thornton) questionnaire** – Helps in classification of ADRs into definitely preventable, probably preventable and not preventable.

5. **Check list:** self-designed list of reported ADR of the chemotherapeutic drugs

4. STUDY PROCEDURE

Patients meeting the inclusion/exclusion criteria were identified during OP and IP visits by investigators, the patients were briefed about the purpose of the study and consent was taken. A self-designed case report form was used to collect the patient demographics, history of illness, diagnostic methods used and laboratory findings through patient interview and additional data was obtained from patient case sheets, treatment charts, and by communicating with the patient, caretaker, and health care providers. Surveillance of ADRs was performed using specifically designed checklist for different chemotherapeutic agents. Characterization of ADR was done by using Naranjo Adverse Drug Reaction Probability Scale, WHO-UMC causality assessment system questionnaire, ADR Severity Assessment Scale (Modified Hartwig and Siegel) questionnaire, and ADR Preventability Assessment Scale (Modified Schumock and Thornton) questionnaire. Additional data, as required, was obtained from patient case sheets, treatment charts, and by communicating with the patient, caretaker, and health care providers. All the information thus obtained were captured on Microsoft Excel®, and analyzed using appropriate statistical methods.

5. RESULT

The present study included 96 patients attending the outpatient clinic and admitted to inpatient wards of the department of oncology in a tertiary care hospital. This study was conducted over a period of three months. Almost all the patients included in the study were females, and only one male patient was enrolled in the study.

Majority of the study patients belonged to the age group of 46-55 (36, 37.5%) followed by the 56-65 years age group (23, 23.95%). Detailed distribution is as in figure 5.1. The average age of the study patients was 51.72 ±10.79 years. The youngest patient included in the study was 34 years old, while the oldest patient was 80 years old.

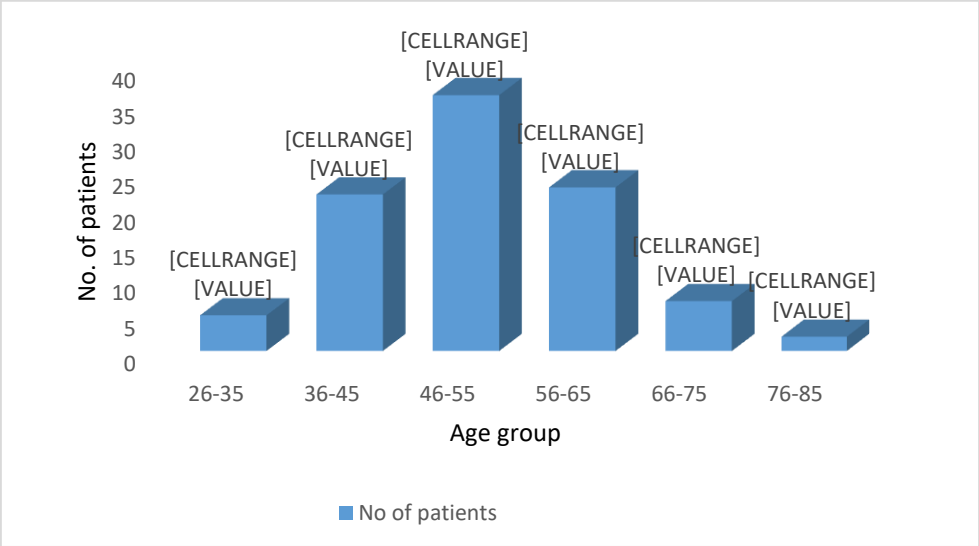

Figure 5.1: Distribution of patients by age group

Majority of the patients (86, 89.58%) presented with invasive ductal carcinoma (IDC) during histopathological examination, followed by 4 patients (4.16%) with invasive lobular carcinoma (ILC). A schematic representation of the findings is illustrated below (Figure 5.2.)

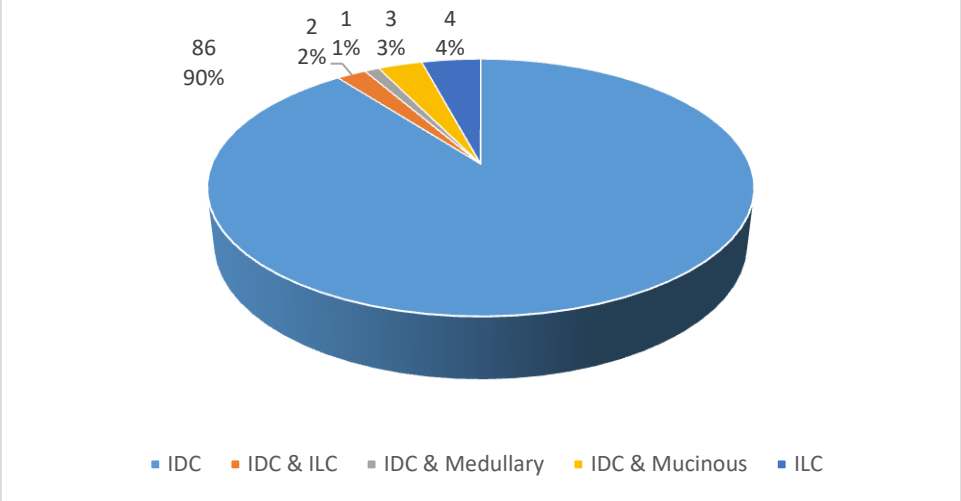

Figure 5.2: Types of cancer among the study population

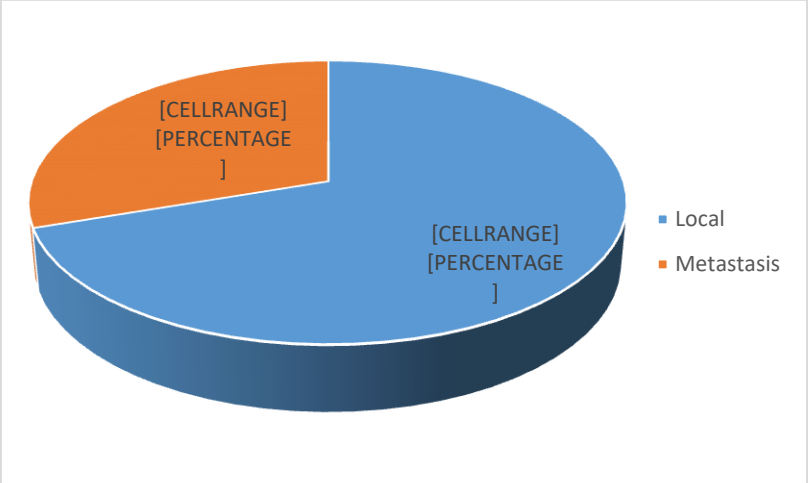

Figure 5.3: Type of tumor among the study population

As shown in the figure above (Figure 5.3), majority of the patients (67, 69.79%) had local carcinoma. Among patients with metastasis (29, 30.00%), most patients (15, 51.72%) had metastasis to more than one organ.

Lung and Bone metastases were the most common (14, 48.28%), followed by Lung (13, 44.83%) and Brain (5, 17.24%). Detailed distribution of organs involved in metastasis is as depicted in Figure 5.4.

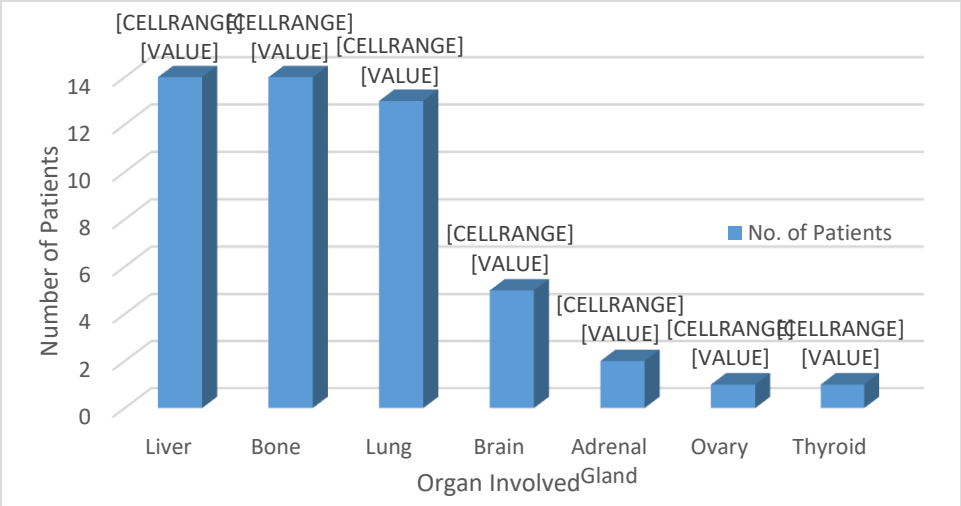

Figure 5.4: Distribution of organs involved in metastasis

The expression of Hormone receptors (Estrogen/Progesterone Receptors) and HER2 gene are important prognostic markers in management of Breast Cancer. They also play an important role in the selection of appropriate chemotherapeutic regimens. Among the study patients, HER2 gene expression was seen in 58 patients (60.42%), while hormone receptors were expressed in 43 patients (44.82%). About 28 patients (29.17%) were positive for all the three prognostic factors – HER2 gene and both the Hormone receptors, and hence were termed as 'Triple Positive'. Detailed distribution is as shown in Table 5.1.

Table 5.1: Distribution of prognostic factors

Prognostic Factor	Distribution	
	n	*%*
Triple Positive	28	30.10
HER2 Positive	23	23.95
Estrogen Receptor Positive	2	2.08
ER+PR Positive	13	13.54
HER2+ER Positive	4	4.30
HER2+PR Positive	3	3.22

**ER – Estrogen Receptor; PR-Progesterone Receptor*

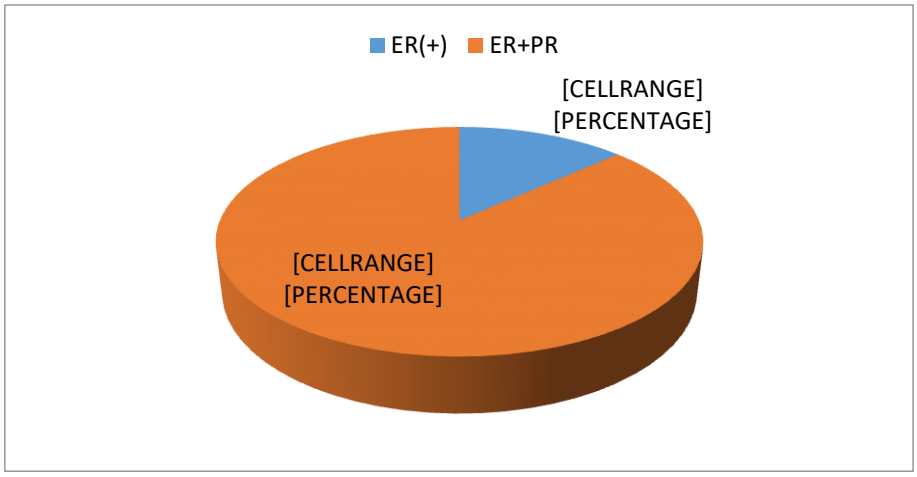

Figure 5.5: Figure showing Hormone receptor status in a study population

In line with the prescribing policies at the study site, patients with HER2 positive status were prescribed a Herceptin containing regimen, premenopausal and postmenopausal women with ER positive treated with SERMs (Tamoxifen) and aromatase inhibitors (Letrozole and Anastrozole) respectively. Detailed distribution is as shown in Table 5.2.

Table 5.2: Distribution of hormone therapy

Type of drug	Distribution	
	n	%
Anastrozole	28	29.16
Letrozole	23	23.95
Tamoxifen	2	2.08
Anastrozole + Letrozole	13	13.54

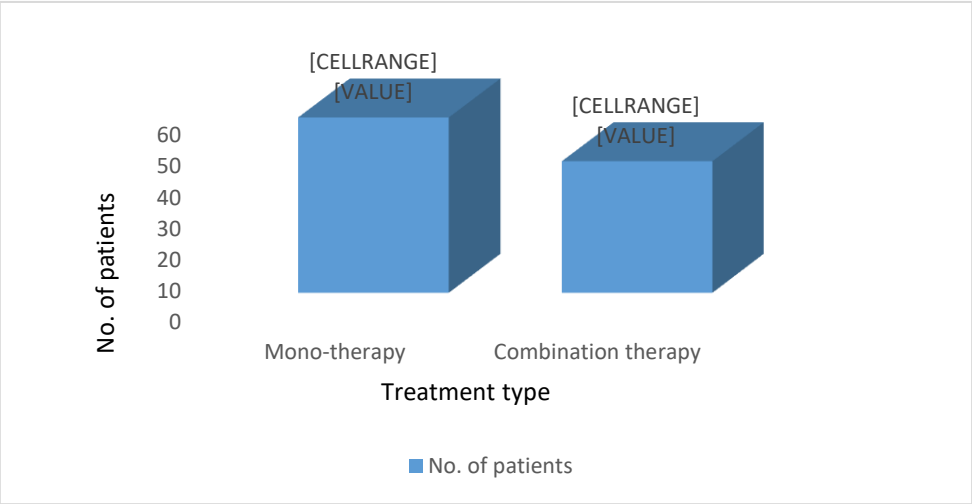

Figure 5.6: Figure showing treatment method used in the study population

As shown in figure 58.33% patients were treated with mono therapy. In which majority of the patients (36, 37.50%) prescribed with Herceptin. The second largest regimen used was docetaxel (19, 19.79%).only one patient (1.04%) was prescribed with paclitaxel. Remaining patients were treated with combination therapies as given in the Figure 5.6

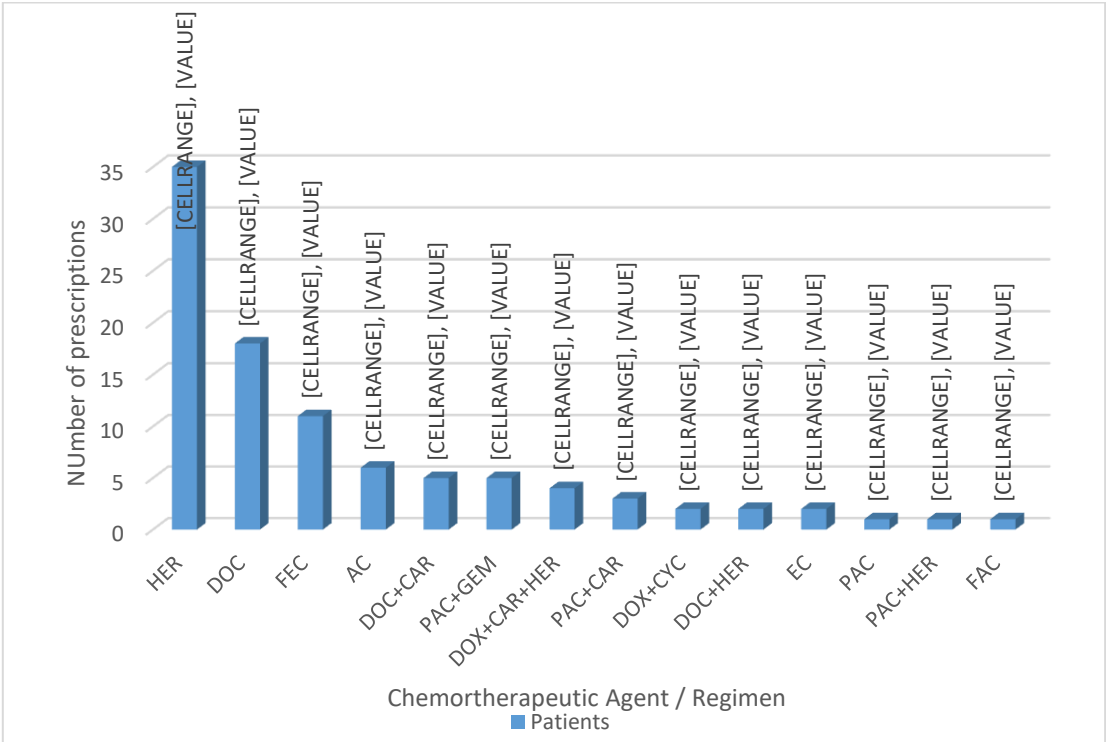

Figure 5.7: Figure showing treatment regimen used in the study population

Out of the 96 patients included in the study, 65 patients (67.71%) developed Adverse drug reactions due to the chemotherapy regimen/agent. Patients developing mild ADRs like Nausea were not considered to have an ADR. While Herceptin and Docetaxel were the most commonly prescribed chemotherapeutic agents (53, 55.21% each) as seen in Figure 5.12, majority of the ADRs were caused by Docetaxel (98, 83.02%) and Cyclophosphamide (93, 25.91%), as seen in Figure 5.8.

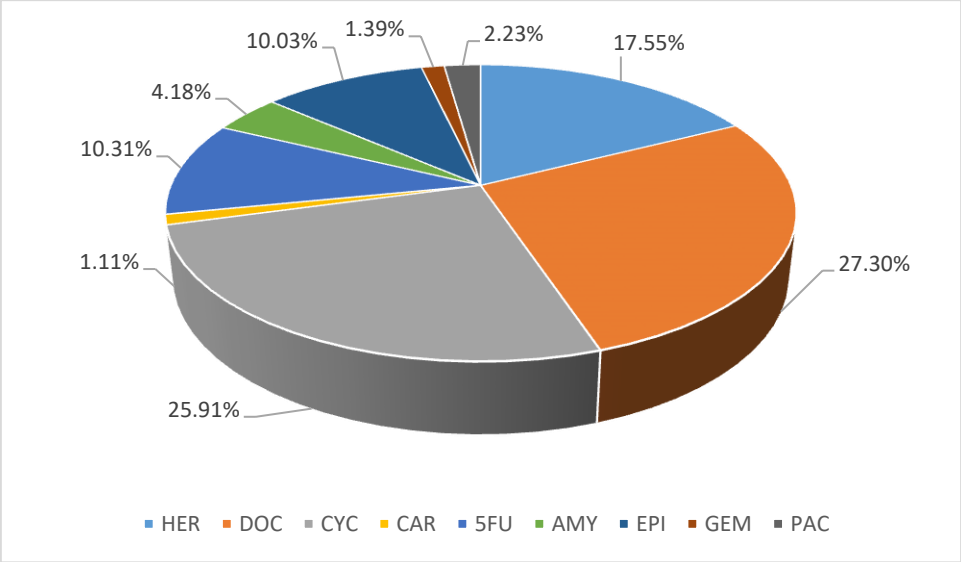

Figure 5.8: Distribution of Adverse Drug Reactions by causative agent

Analysis of adverse drug reaction by the causative agent shows that Carboplatin caused ADRs in 96.15% patients prescribed with the agent, while Paclitaxel caused ADRs in only 40% of the patients. Herceptin and Docetaxel, the most prescribed chemotherapeutic agents, caused ADRs in 77.36% and 83.02% agents respectively. Detailed distribution is presented in Figure 5.9.

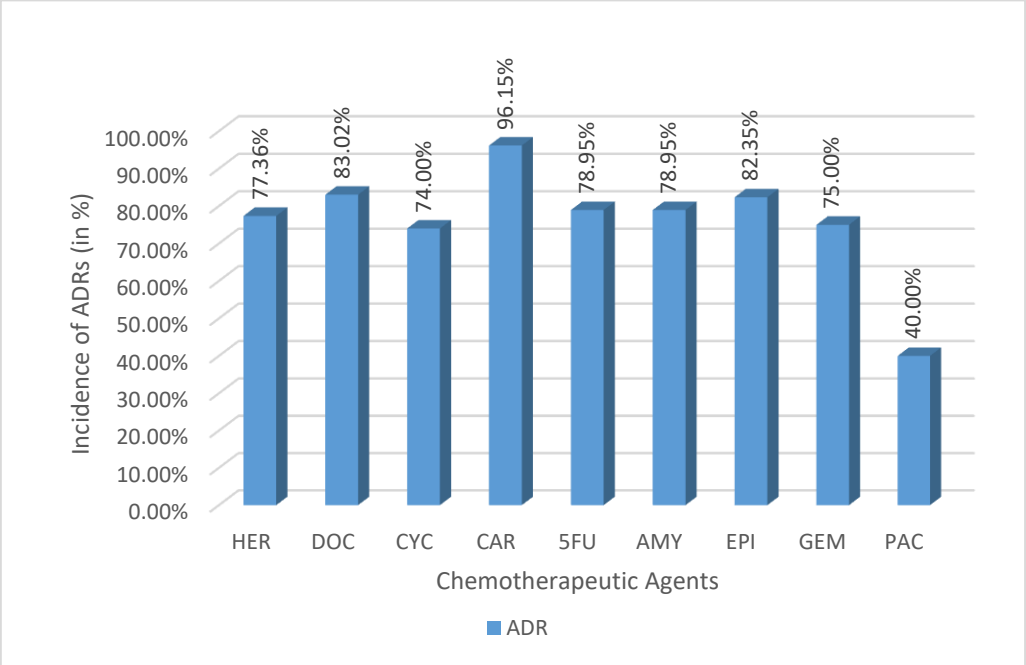

Figure 5.9: Distribution of incidence of ADRs by causative chemotherapeutic agent

As seen in Figure 5.9, Herceptin was the most prescribed chemotherapeutic agent (either for monotherapy or for combination therapy). Herceptin caused ADRs in 77.36% of the patients receiving the agent (Figure 5.9). The most common ADR caused by Herceptin was Anorexia (8, 15.09%), and the second most common ADR was discolouration of nail (7, 13.21%), as seen in Figure 5.10.

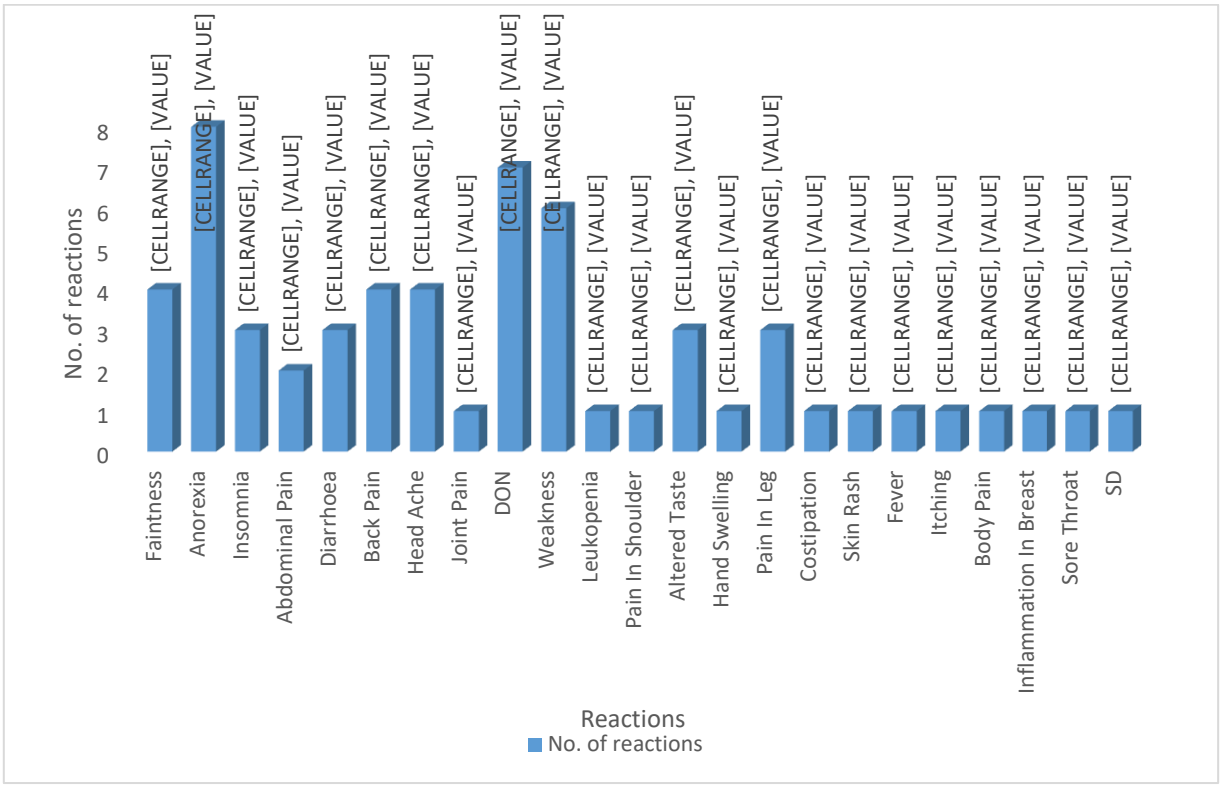

Figure 5.10: Distribution of ADRs caused by Herceptin

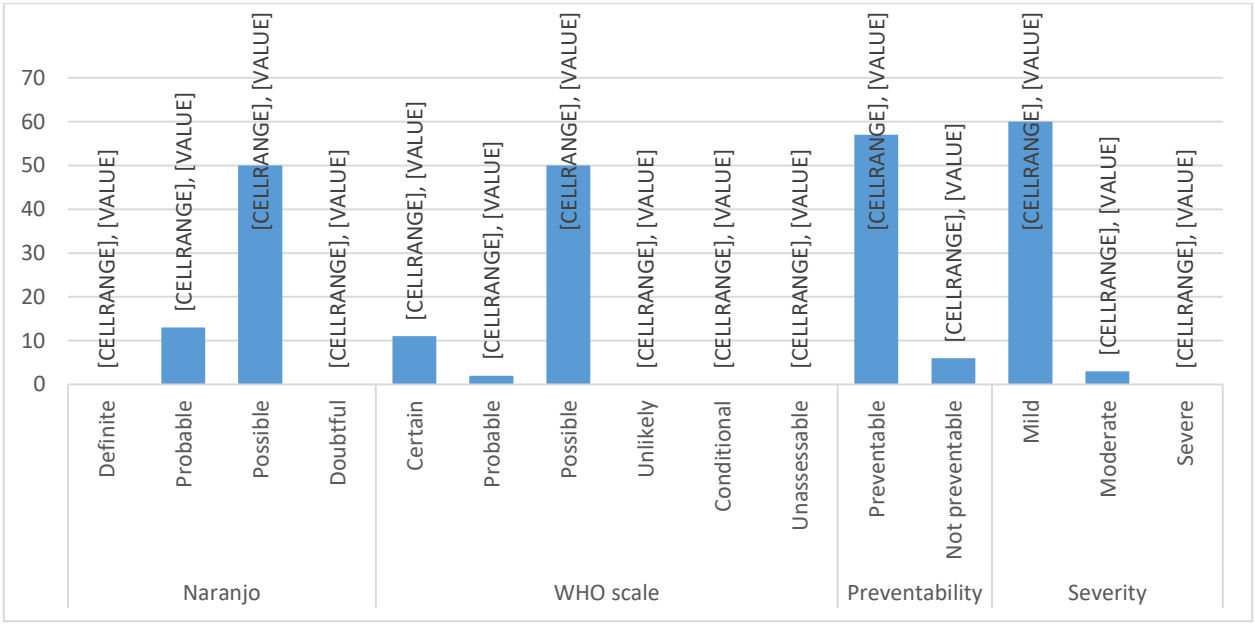

Figure 5.11: Characterization of ADRs caused by Herceptin

Figure 5.11 shows the characterization of ADRs caused by Herceptin. Majority of the ADRs caused by Herceptin were preventable (90.48%) and mild (95.24%). Causality assessment shows that most of the ADRs were possible (79.37%).

Docetaxel caused ADRs in 83.02% of patients receiving the agent (Figure 5.8.) the most common ADR caused by docetaxel was discoloration of nail (DON) (14, 26.42%) and the second most ADR was Anorexia (11, 20.75%), as seen in Figure 5.12.

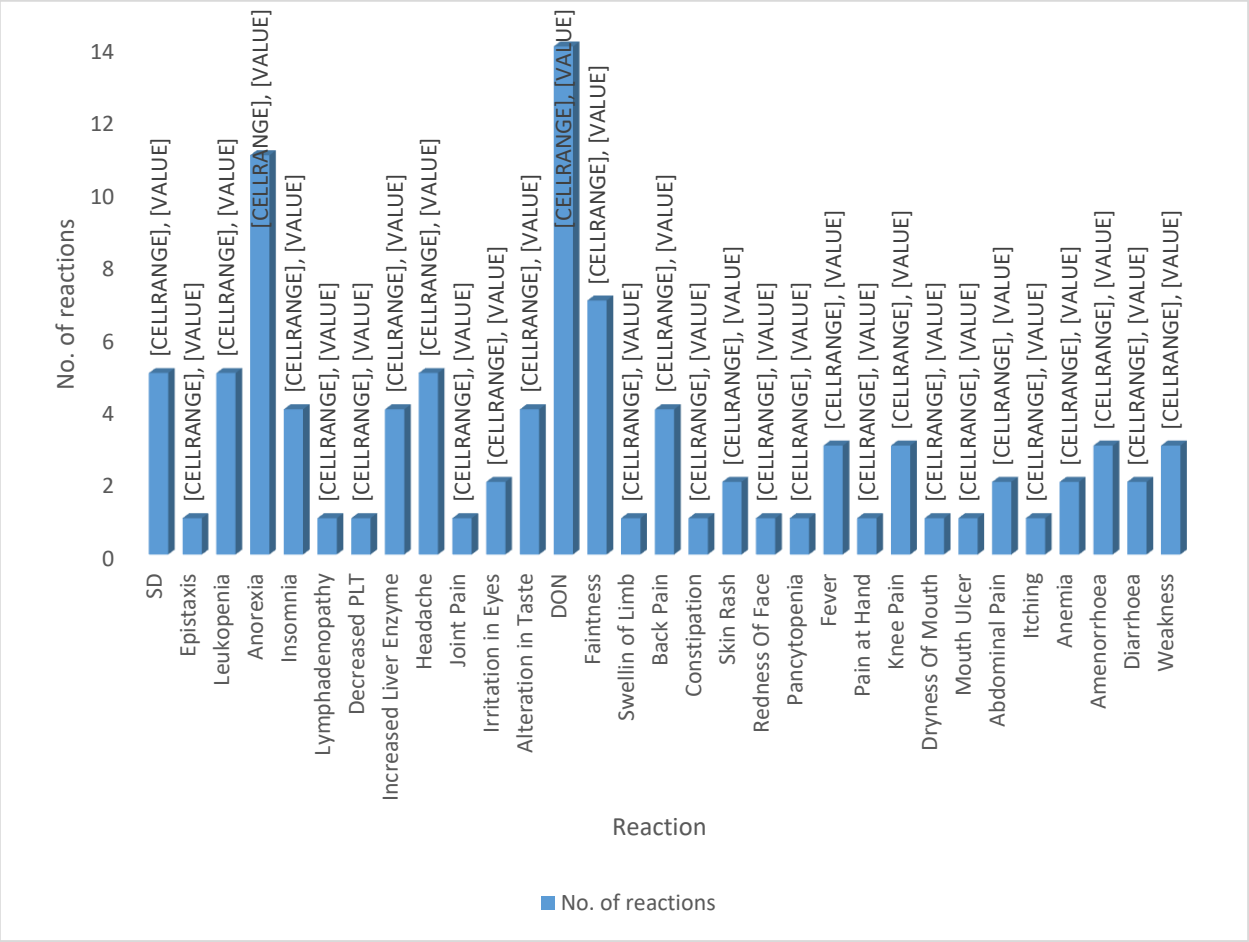

Figure 5.12: Distribution of ADRs caused by Docetaxel

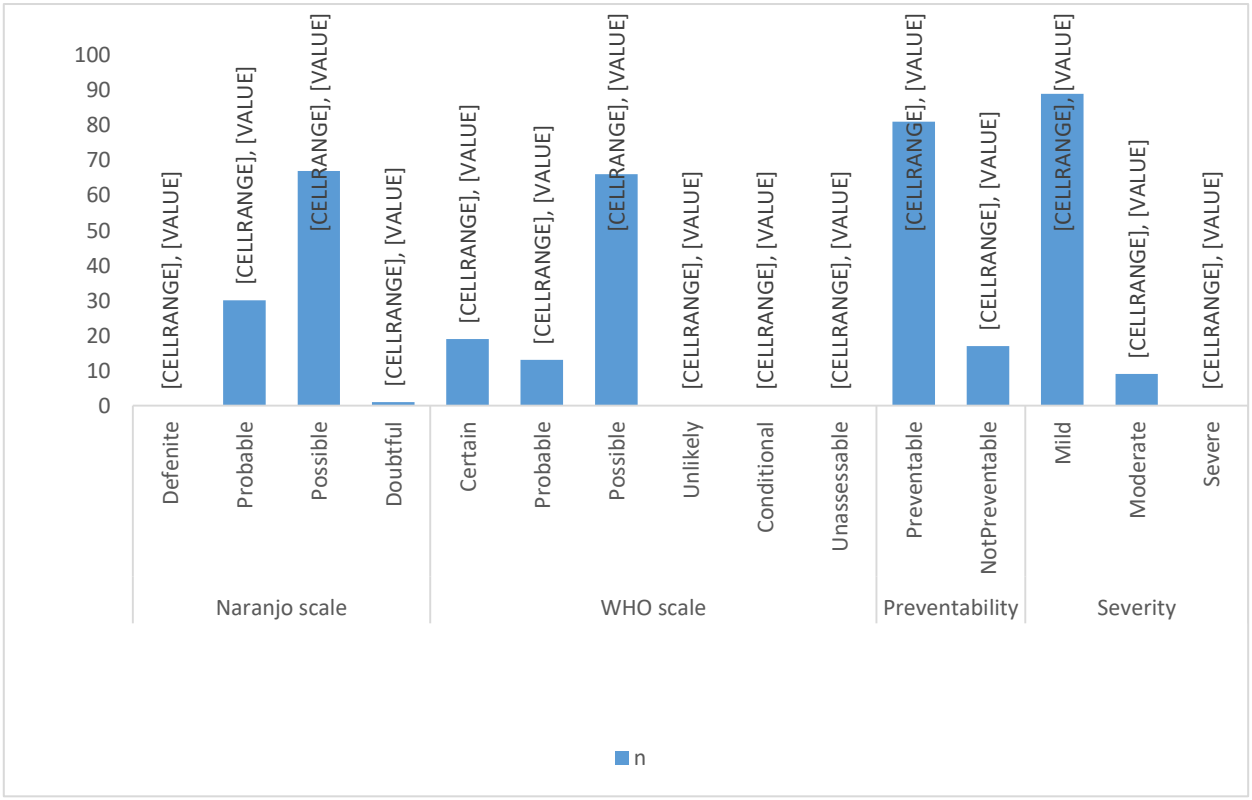

Figure 5.13: Characterization of ADRs caused by Docetaxel

Figure 5.13 shows the characterization o ADRs caused by Docetaxel. Majority of the ADRs caused by Docetaxel were preventable (81, 82.67%), and mild (89, 90.82%). Causality assessment shows that most ADRs were possible according to Naranjo (67, 68.35%) and WHO (66, 68.37%) scales.

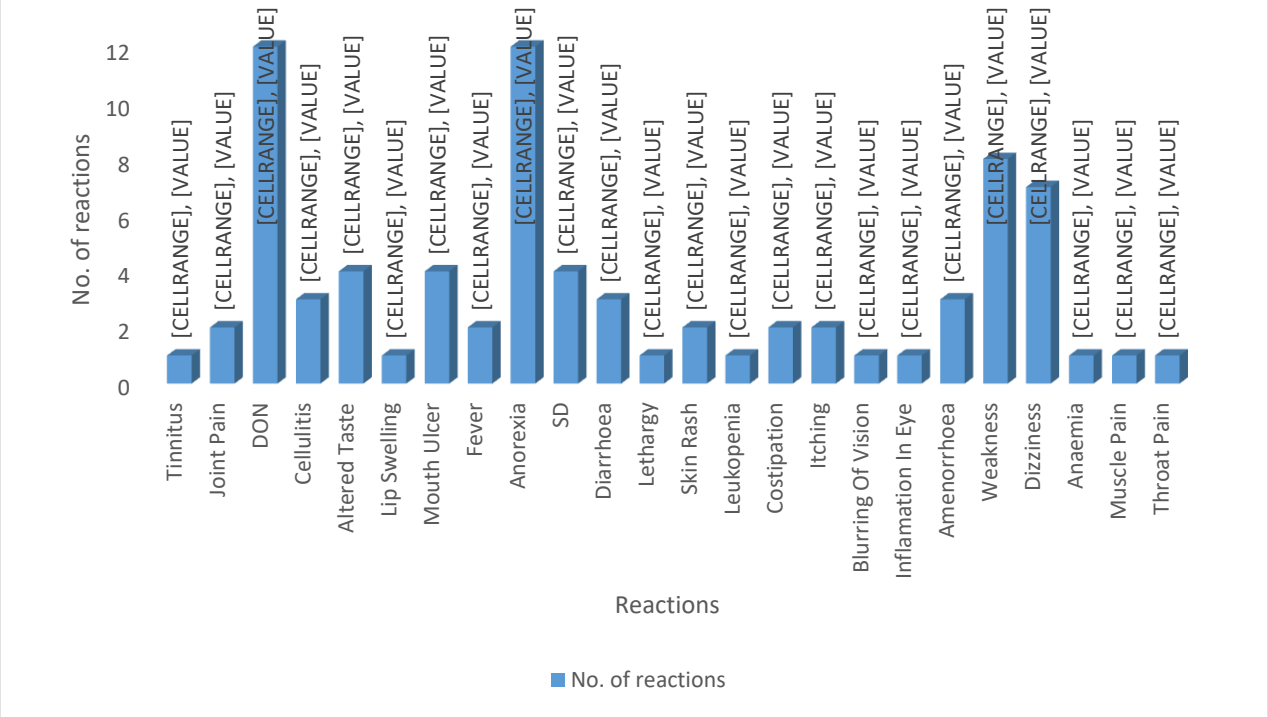

Figure 5.14: Distribution of ADRs caused by Cyclophosphamide.

About 74.00% patients developed ADRs on Cyclophosphamide therapy. The most common ADRs caused by Cyclophosphamide were discoloration of nail and anorexia (12, 24.00%), as shown in Figure 5.14. Majority of ADRs (87, 93.55%) caused by Cyclophosphamide were preventable (87, 93.55%) and Mild (85, 91.45%). About 72(77.40%) ADRs were possible according to Naranjo scale and 73(78.49%) ADRs were possible according to WHO scale, as seen in Figure 5.15

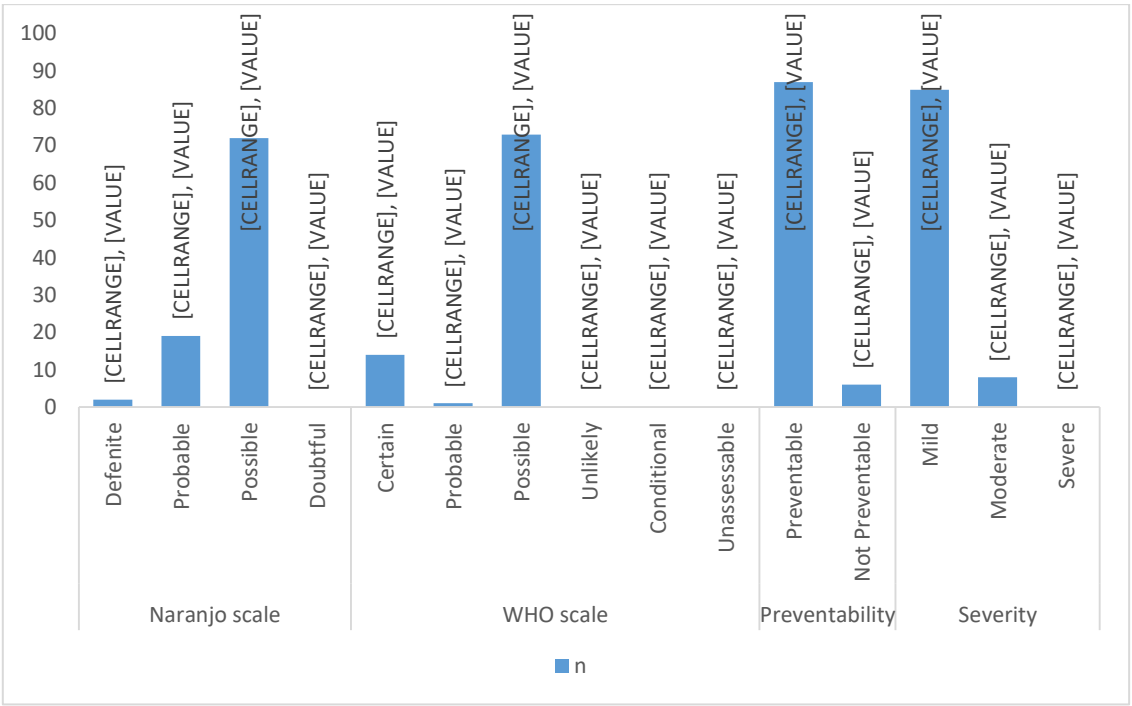

Figure 5.15: Characterization of ADRs caused by Cyclophosphamide

5-Flurouracil caused ADRs in 78.94 of patients receiving the agent (Figure 5.14) the most common ADR caused by 5-Flurouracil was Anorexia (7,18.42%) and the second most ADR was discolouration of nail (6, 15.79%), as seen in Figure 5.16

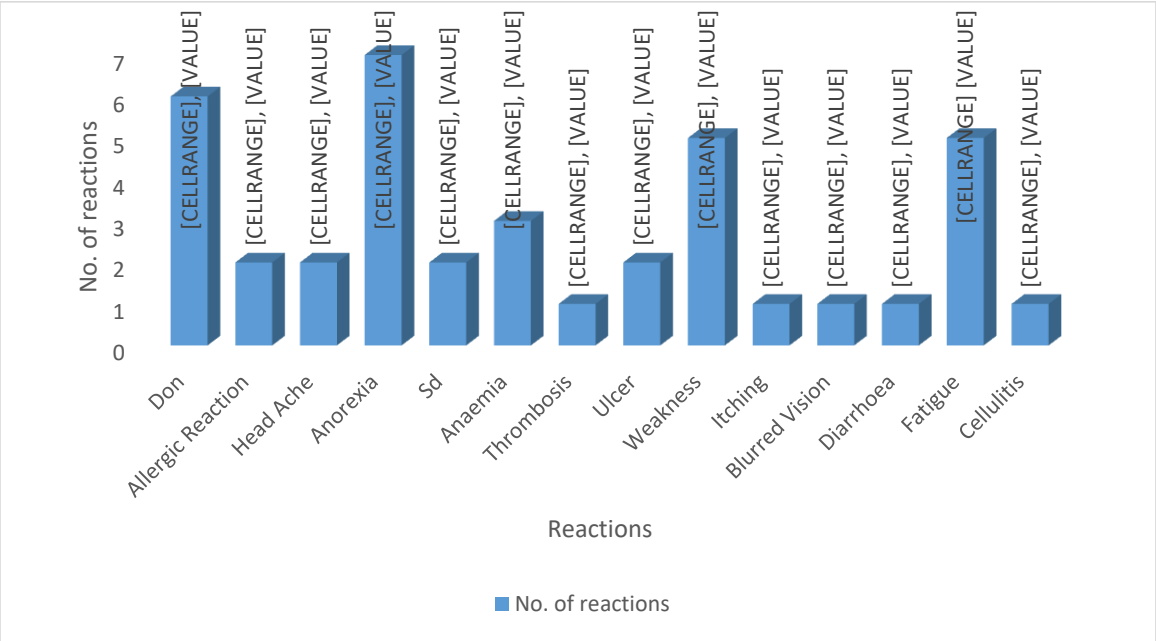

Figure 5.16: Distribution of ADRs caused by 5-Flurouracil

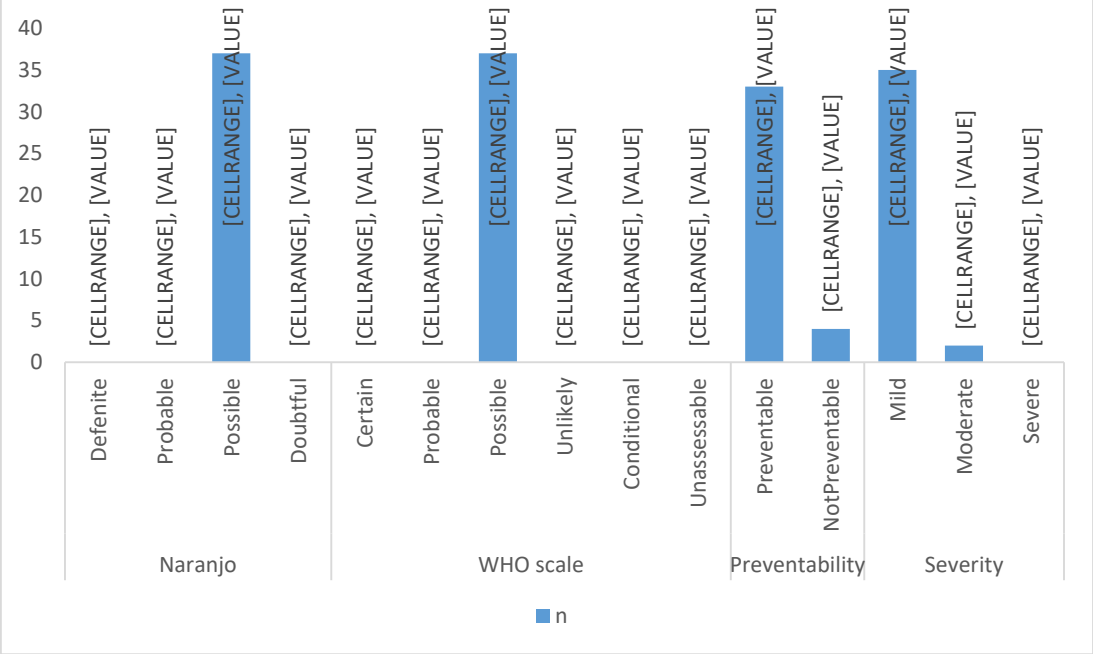

Figure 5.17: Characterization of ADRs caused by 5-Flurouracil

Figure 5.17 shows the characterization o ADRs caused by 5-Flurouracil. Majority of the ADRs caused by 5-Flurouracil were preventable (33, 89.18%), and mild (35, 94.59%). Causality assessment shows that all the ADRs (37,100%) were possible.

About 82.35% ADRs were reported by patients on Epirubicin therapy. Among these ADRs, majority were Dizziness (6,17.65%) and second most common ADRs were anorexia and weakness (4,11.76%), as seen in Figure 5.18.

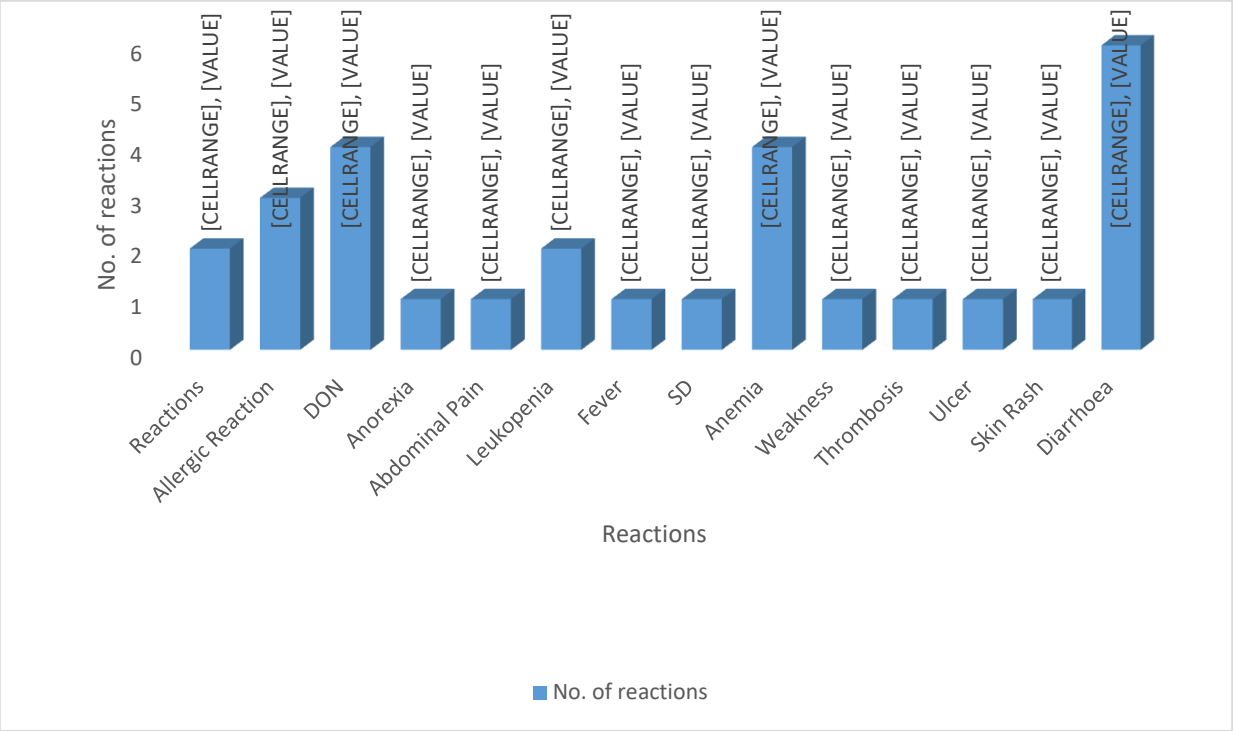

Figure 5.18: Distribution of ADRs caused by Epirubicin

Majority of ADRs reported by Epirubicin were preventable (27, 75.00%) and mild (29,80.56%). Causality assessment shows majority of ADRs were possible according to Naranjo scale (34,94.44%) and WHO scale (35,97.22). Detailed distribution seen in Figure 5.19.

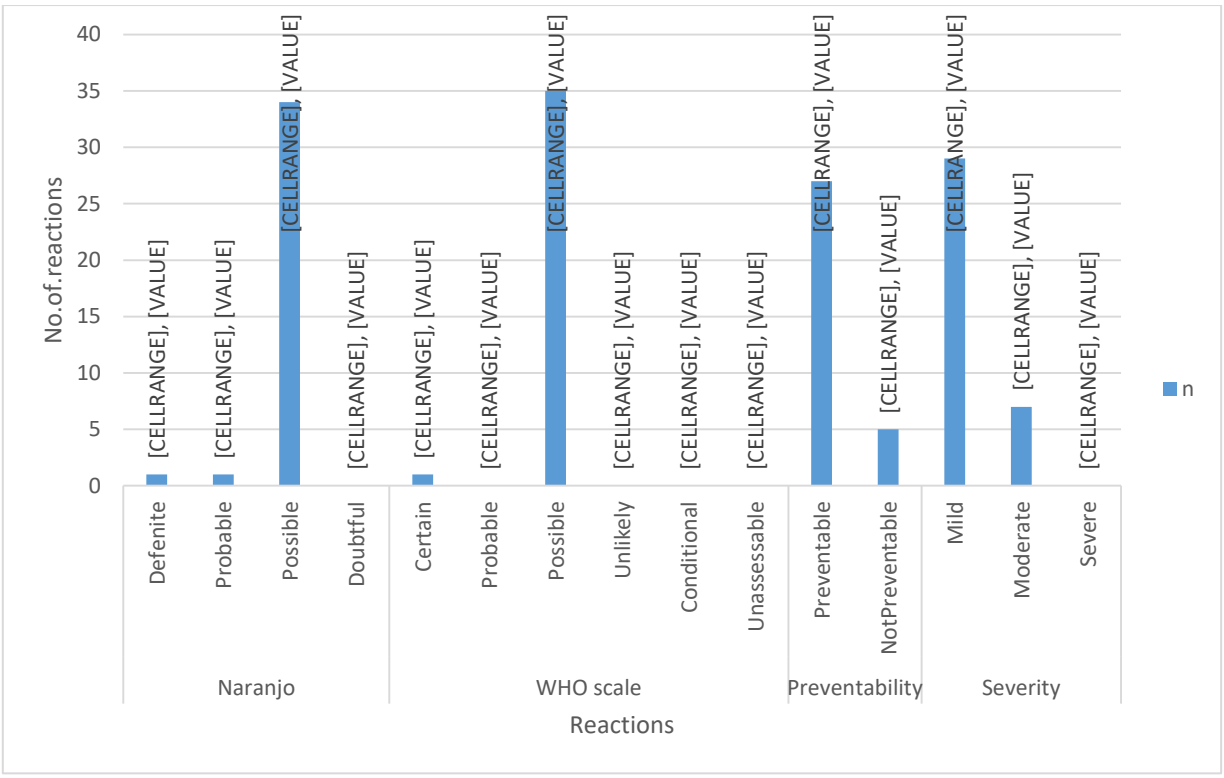

Figure 5.19: Characterization of ADRs caused by Epirubicin

Carboplatin caused ADRs in 96.15% of patients receiving the agent (Figure 5.9.). The incidence of all the ADRs were same, as shown in Figure 5.20. Among the ADRs 2 (50%) of ADRs were preventable and 3(75%) were mild. All the ADRs were possible in causality assessment (Figure 5.21)

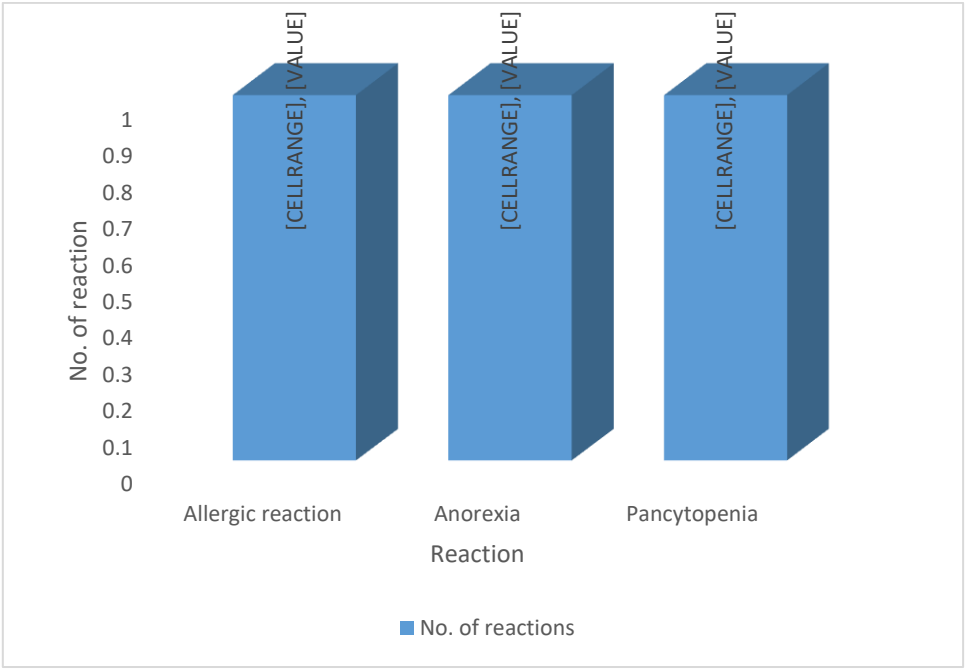

Figure 5.20: Distribution of ADRs caused by Carboplatin

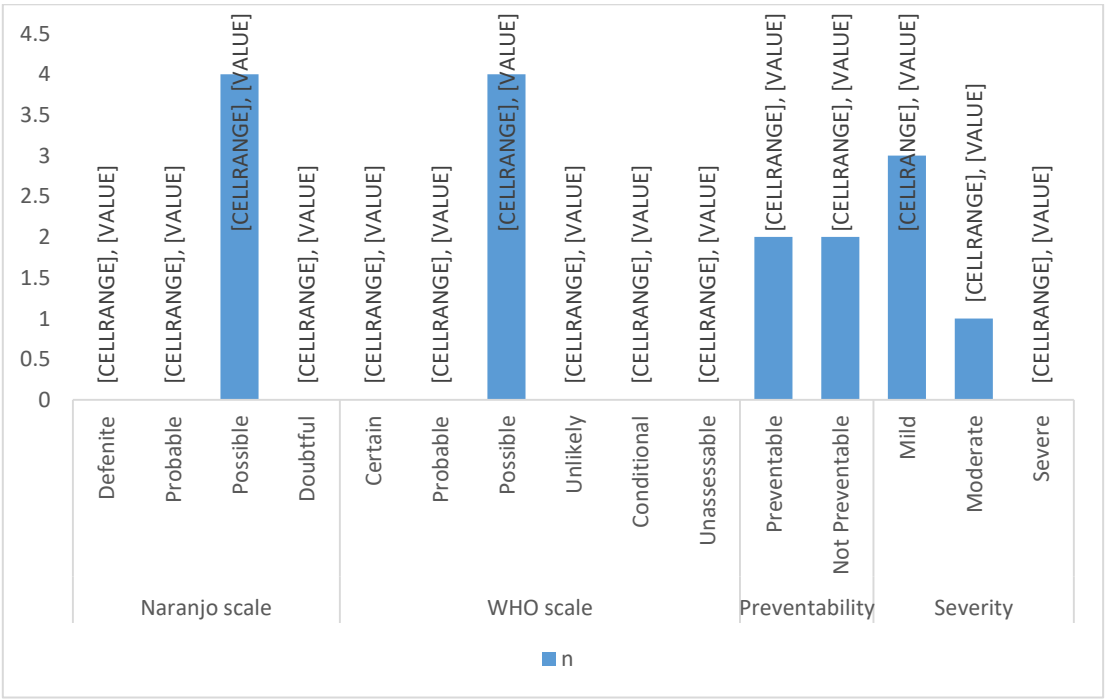

Figure 5.21: Characterization of ADRs caused by Carboplatin

Adriamycin caused ADRs in 78.94% of patients receiving the agent (Figure 5.9.). The most common ADR caused by Adriamycin was anorexia (3, 79.3%) and the second most ADR was Dizziness (2, 10.53%), as seen in Figure 5.22

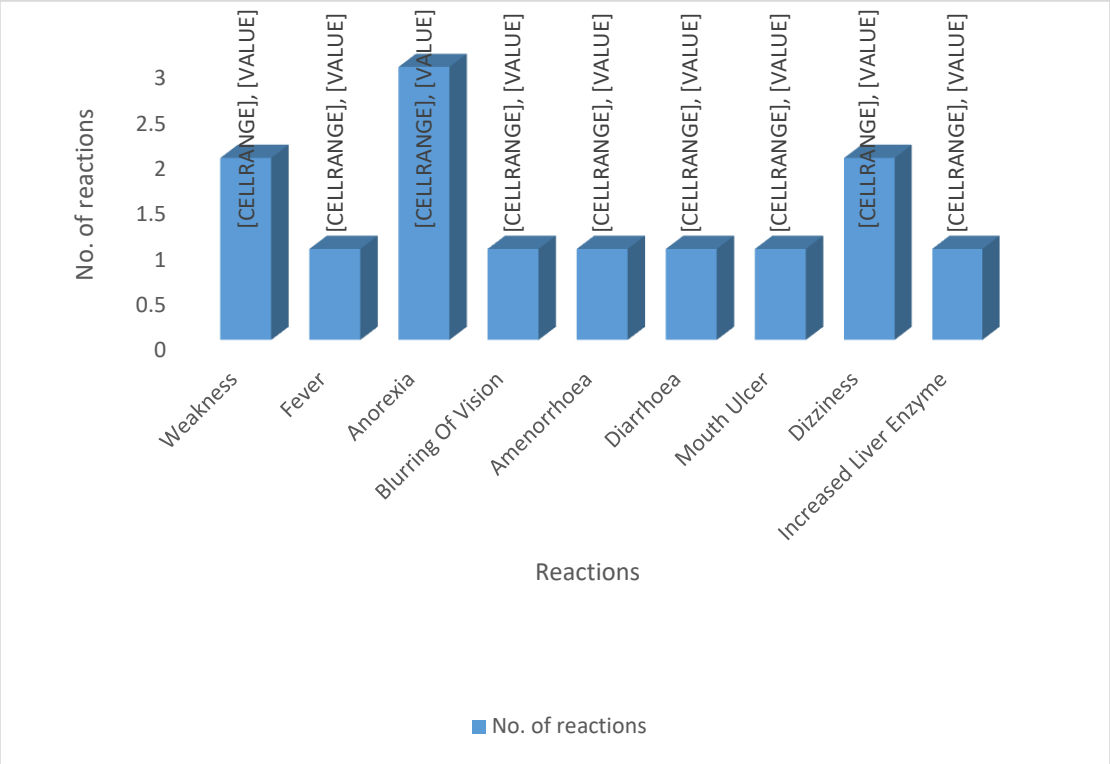

Figure 5.22: Distribution of ADRs caused by Adriamycin

All the ADRs caused by Adriamycin were mild and majority of the ADRs were preventable (13, 86. 67%). Causality assessment shows that all the ADRs were possible, as seen in Figure 5.23

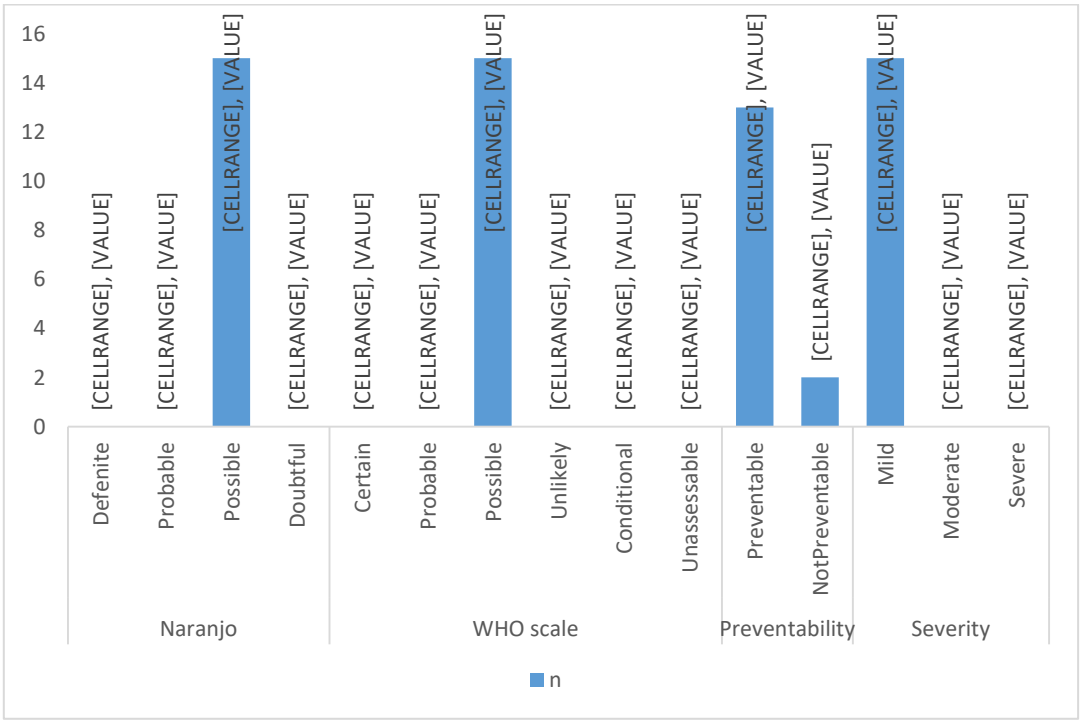

Figure 5.23: Characterization of ADRs caused by Adriamycin

Paclitaxel caused ADRs in 40.00% of patients receiving the agent (Figure 5.9.) the most common ADR caused by Paclitaxel was weakness (2, 50.00%). Detailed distribution is given in Figure 5.24. All the reported ADRs were mild and majority of them were not preventable (7,87.50%). All the ADRs were possible according to Naranjo scale and certain according to WHO scale, as shown in Figure 5.25

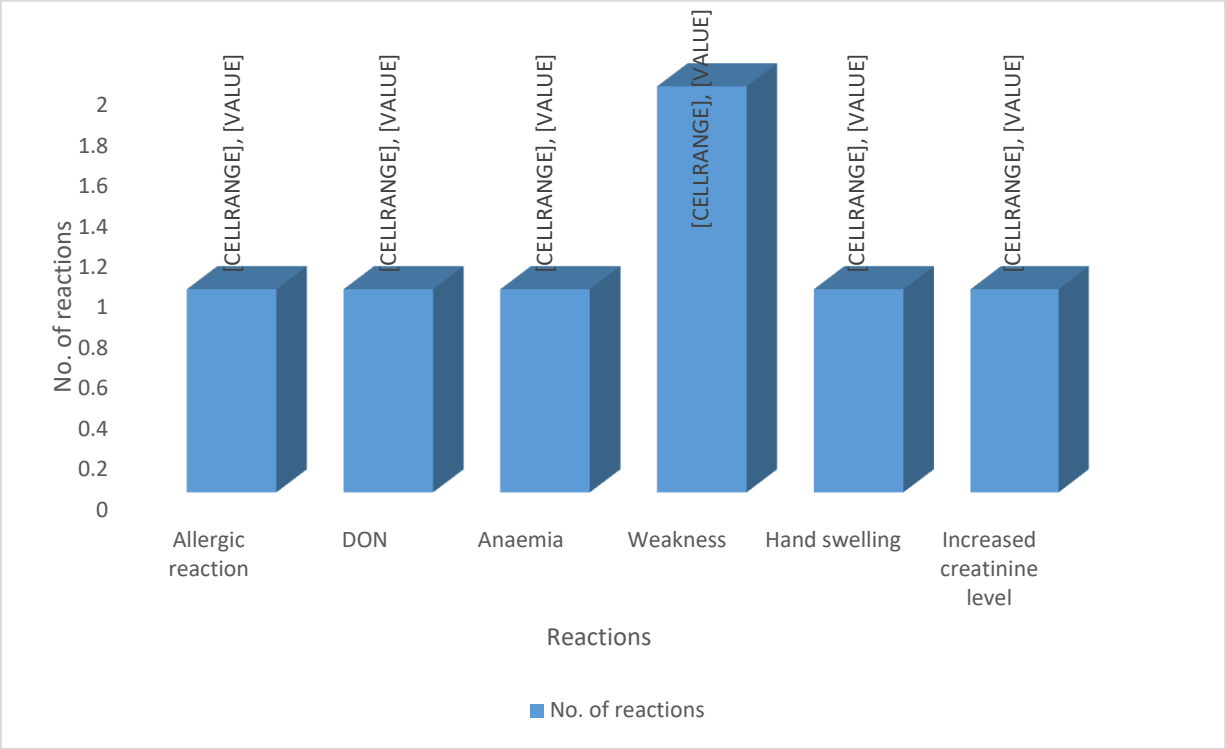

Figure 5.24: Distribution of ADRs caused by Paclitaxel

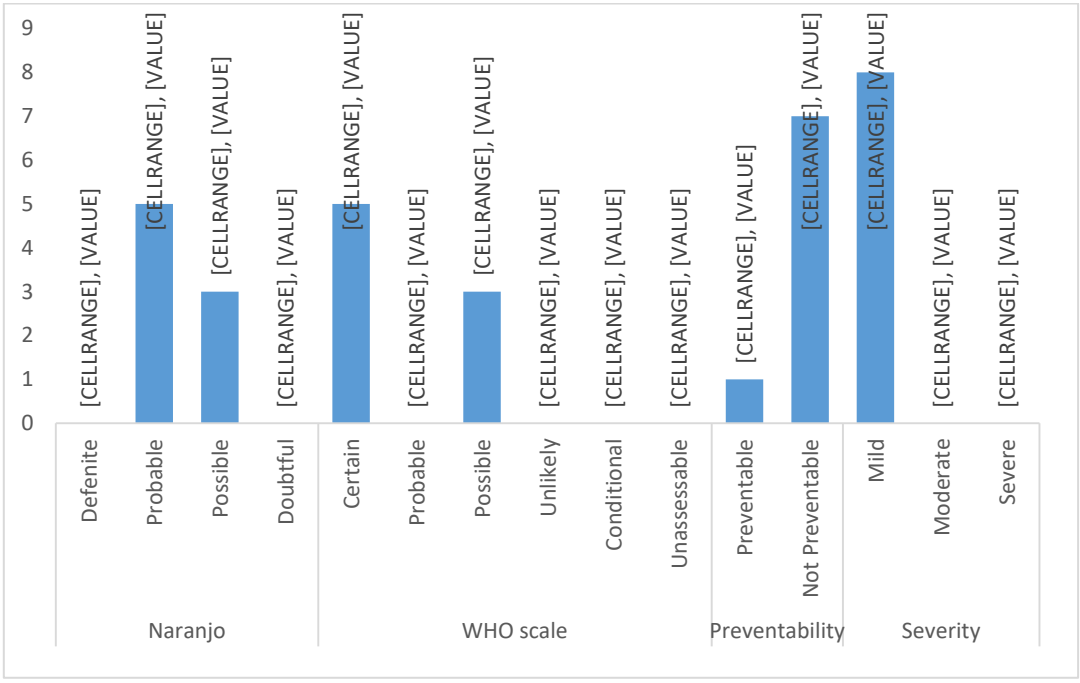

Figure 5.25: Characterization of ADRs caused by Paclitaxel

Gemcitabine caused ADRs in 75.00% of patients receiving the agent (Figure 5.9.). The most common ADR caused by Gemcitabine was anorexia (2,50.00%). Detailed distribution given in Figure 5.26

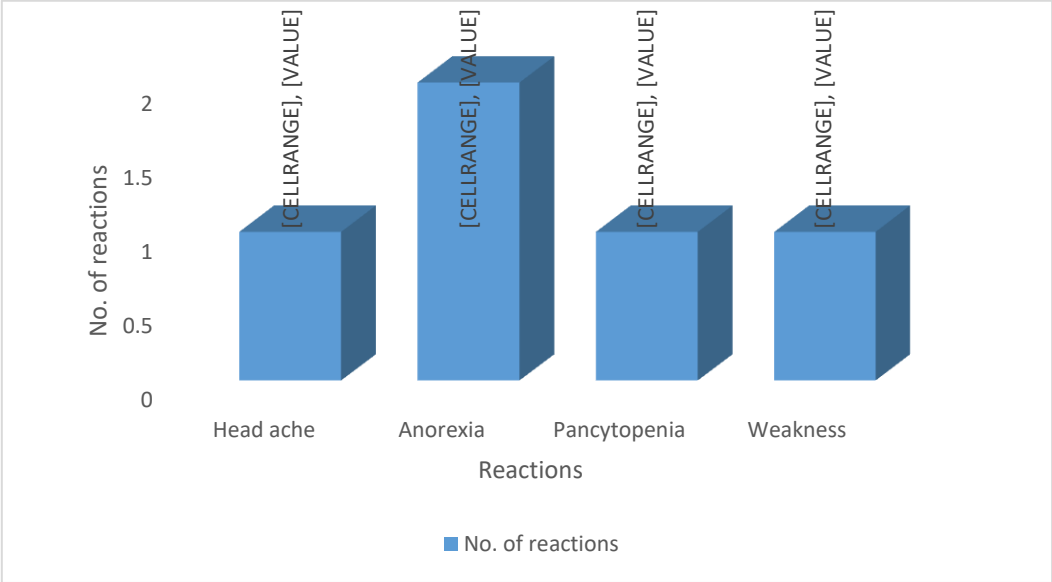

Figure 5.26: Distribution of ADRs caused by Gemcitabine

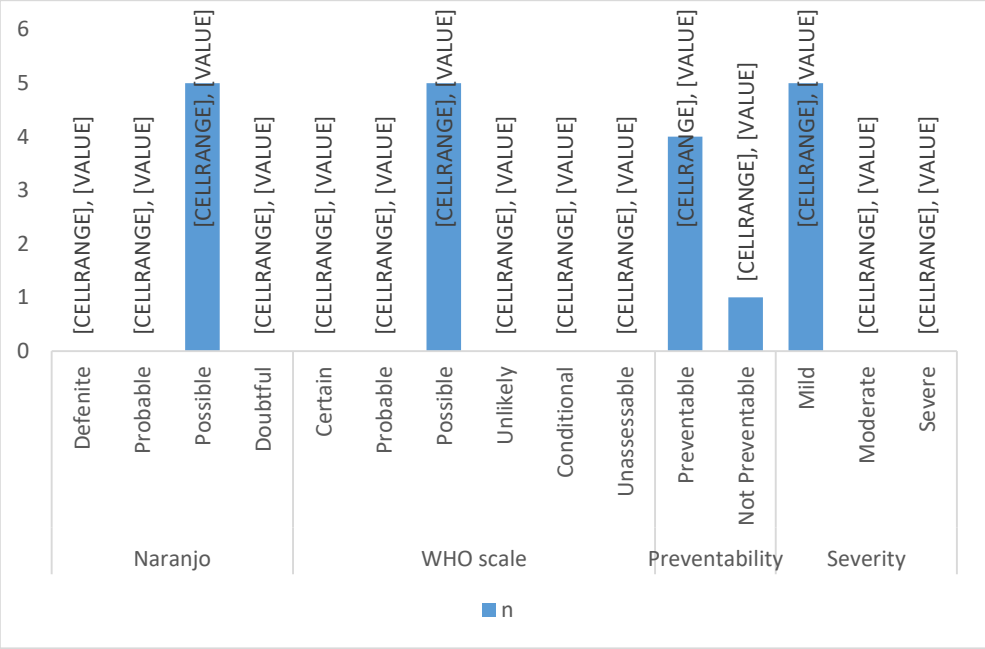

Figure 5.27: Characterization of ADRs caused by Gemcitabine

Figure 5.27 shows the characterization of ADRs caused by Gemcitabine. All the ADRs caused by Gemcitabine were mild (5, 100%) and majority of the ADRs were preventable (4, 80.00%) Causality assessment shows that all the ADRs were possible.

All the patients enrolled in the study were treated with prophylactic regimen for nausea/vomiting, fever, restlessness/anxiety, diarrhea and gastritis. About 31 patients presented with nausea/vomiting even after taking prophylactic regimen. Among them 15 (51.61%) were treated with Herceptin.

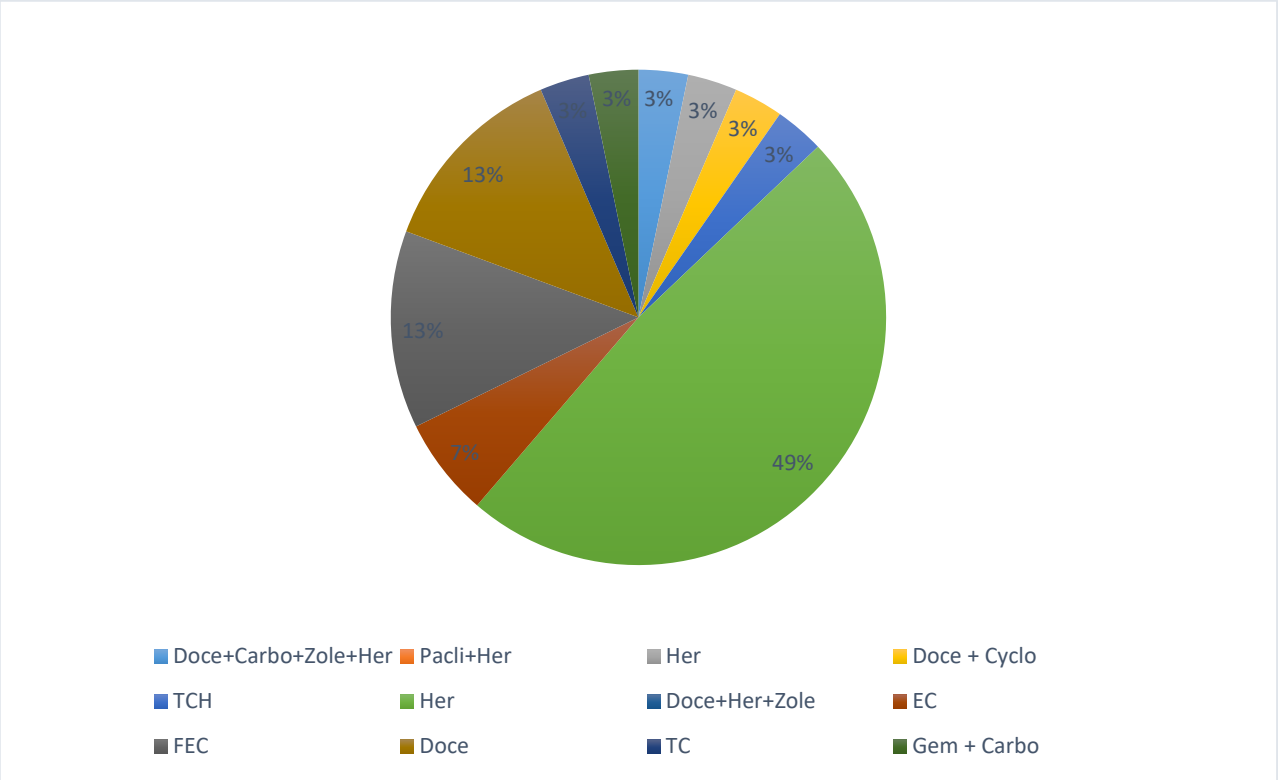

Figure 5.28: Figure showing incidence of ADR after prophylaxis

6. DISCUSSION

This study was conducted in the outpatient clinic and inpatient wards of the department of tertiary care Hospital. In the present study, majority of the patients (38 %) belonged to the age group of 46-55. The average age of the study patients was 51.94±10.79. The youngest patient included in the study was 35 years, while the oldest was 80 years. This finding was similar to the study performed by **Chopra B *et al.***[4]

Triple Positive status (presence of both hormone receptors are HER2 gene expression) was seen in 30.10% of the patients. They were treated with Chemo hormonal therapy. While 52 % patients were positive for hormonal receptors and majority of these patients were 40 years or older. This finding was disparate from the result of the study done by ***Pourzand A et al***, which says that there is a direct correlation between positive progesterone receptor status and being younger than 40. Furthermore, this study includes patients with negative progesterone receptor status who were more likely to have HER-2 overexpression which was similar to result of study conducted by ***Pourzand A et al.***[5]

Present study pattern of ADRs were assessed by using Naranjo Adverse Drug Reaction Probability Scale questionnaire, WHO-UMC causality assessment system questionnaire, Modified Hartwig and Siegel questionnaire and Modified Schumock and Thornton questionnaire. In the present study, multiple ADRs were seen in patients who experienced ADRs. Most of them were predictable, of mild-to-moderate severity, non-serious, and preventable. A majority of the ADRs recovered over times. These findings were similar to the result of the study conducted by ***Singh S et al.***[6]

In this study, majority of the patients were prescribed with Herceptin and Docetaxel (53, 55.21% each). Among the patients receiving Herceptin 77.36% were reported to have ADRs. The most common ADR caused by Herceptin was Anorexia (8, 15.09%), and the second most common ADR was discoloration of nail (7, 13.21%). No patients were reported with cardiac dysfunctions such as ventricular dysfunction and congestive heart failure which was significant complication associated with Herceptin according to ***Gemmete J.J et al*** [7]

Meanwhile, majority of the ADRs were caused by Docetaxel (98, 83.02%), the finding is similar to the study conducted by E**. Hall *et al.*,** on QoL and toxicity which showed a clear evidence of women's exposure to greater toxicity and disruption to different aspects of their QoL over many months from Taxanes-containing treatment compared to standard adjuvant chemotherapy. The most common ADR caused by docetaxel in this study was discoloration of nail (DON) (14, 26.42%) and the second most common ADR was Anorexia (11, 20.75%). Majority of the ADRs experienced possible

according to Naranjo (67, 68.35%) and WHO (66, 68.37%) causality assessment scale, about 81, 82.67%), and (89, 90.82%) ADRs were mild and preventable respectively.[8]

Present study showed that prescribed carboplatin caused ADRs in 96.15% patients and was found to be the major causative agent according to the analysis. The most common ADRs caused by carboplatin were allergic reaction, pancytopenia, and anorexia. All ADRs were possible, among which 2 (50%) were preventable and 3(75%) were mild.

Meanwhile ADRs caused by Cyclophosphamide were discoloration of nail and anorexia (12, 24.00%). Among which most of them were possible and mild. Majority of the ADRs were preventable.

Only 40% of patients experienced ADR caused by paclitaxel. Majority of them were not preventable, while all the ADRs were possible according to Naranjo scale and certain according to WHO scale.

Present study had shown that Gemcitabine and Adriamycin causes anorexia in majority (3, 79.3%) of patients, characterization of ADRs concluding majority of the ADRs were possible, preventable and mild. The Patients who received 5-FU as combination therapy had anorexia as common ADR. Majority of the ADRs caused by 5-Flurouracil were preventable, and mild. Causality assessment shows that all the ADRs (37,100%) were possible. About 82.35% ADRs were reported in Epirubicin therapy, among which majority were Dizziness. The ADRs were mild, preventable and possible.

7. CONCLUSION

The study was conducted in a tertiary care hospital in Bengaluru. Patients were enrolled from outpatient clinic and inpatient wards of the department of Oncology. The average age of the study patients was 51.94±10.79 years.

Patients were treated with monotherapy and combination therapy. Herceptin and Docetaxel were the most commonly used chemotherapeutic agent among the study patients. Among the patients who developed ADRs, majority were due to docetaxel and cyclophosphamide. Anorexia, Discoloration of nail, Dizziness and Allergic reactions were the most commonly developed ADRs. Majority of them were preventable, mild and possible in nature, except weakness which was caused by Paclitaxel, was not preventable.

All the patients in the study were treated with prophylactic regimen for nausea/vomiting, fever, restlessness/anxiety, diarrhea and gastritis with Ondansetron, Paracetamol, Alprazolam, Lactobacillus and Pantoprazole respectively. Few patients presented with nausea/vomiting despite taking prophylactic regimen. Majority of such patients were on a Herceptin containing regimen.

Chemotherapeutic drugs have narrow therapeutic index and contribute significantly to the global burden of ADRs3. Categorization of ADRs according causality, preventability and severity will give information that can guide physicians for selecting the best therapy among available drugs.

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