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Adverse Drug Reactions in Non-Metastatic Breast Cancer Patients Treated with Anthracycline-Taxane and +/- Carboplatin and/or +/- Trastuzumab-based Regimens: A Prospective Cohort Study from Tertiary Care Teaching Hospital, South India

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Abstract

Background and objectives: Chemotherapy is the standard treatment for Non-metastatic breast cancer. All the chemotherapeutic agents are capable of producing various Adverse Drug Reactions (ADR) in heterogeneous organs of the body. In this prospective cohort study, we assessed whether ADRs from three different chemotherapy regimens varies in patients with Non-metastatic breast cancer.

Methods: Patients who satisfied eligibility criteria were enrolled and divided into three groups based on the chemotherapy regimen they had taken. The patients who received doxorubicin and cyclophosphamide (AC) followed by Docetaxel (T) were assigned to group AC-T, those who received AC followed by Docetaxel and carboplatin (Cb) were in group AC-TCb and those who received AC followed by Docetaxel and Trastuzumab (H) were assigned to group AC-TH. ADR reported by patients as well as from laboratory reports were Graded as per NCI CTCAE guidelines.

Result and discussion: A total of 190 patients were enrolled of which, 84 patients (44.2%) received AC-T, 52 (27.4%) AC-TCb and 54 (28.4%) AC-TH regimen. Among thirteen system organ classification studied, general disorder was statistically significant (P value=0.012). Grade 3/4 hand-foot syndrome was present in 3 subjects from AC-T and 1 from AC-TCb. Vomiting, Grade 4 type was 1 from AC-T and AC-TCb had. One from AC-TCb had constipation, Grade 3. Mucositis Grade 4 type was observed from both AC-T and AC-TCb. One from AC-TCb had diarrhea, Grade 3. Although hematological reactions were a few but most of them belongs to severe type. 3 from AC-T, 1 from AC-TCb and 2 from AC-TH had anemia, Grade 3/4. 9 subjects from AC-T, 5 from AC-TCb and 4 from AC-TH had febrile neutropenia, Grade 3/4. 19 subjects from AC-T, 12 from AC-TCb and 11 from AC-TH had neutropenia, Grade 3/4. 14 subjects from AC-T, 8 from AC-TCb and 7 from AC-TH had insomnia, Grade 3/4. One subject from AC-T had hearing impaired, Grade 4.

Conclusion: All regimens tolerated by the subjects reasonably very well with majority of adverse effects were mild. Severe (Grade 3 or 4) adverse effects were rare.

Keywords: Breast cancer; Doxorubicin; Cyclophosphamide; Docetaxel; Carboplatin; Trastuzumab; Adverse drug reaction; NCI CTCAE

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Introduction

In this era, breast cancer denotes one of the most common female cancer in both the developing and developed world, and the primary cause of mortality among women [1,2]. Approximately 1,45,000 new cases of breast cancer cases were reported from India in 2012 as per Globocon Global Cancer Registry 2012, and 70,218 patients died due to this malignancy [3]. An increase in breast cancer cases were also reported from Kerala. In the study site 503 cases of breast cancer were registered out of 4621 total cancer registries in the year 2016 alone.

Adjuvant chemotherapy was the primary systemic treatment for breast cancer. But now neoadjuvant chemotherapy is the standard treatment of choice for Locally Advanced Breast Cancer [4]. CMF (Cyclophosphamide, Methotrexate, 5-fluorouracil) was the standard treatment earlier but was replaced by Anthracyclines due to extensive ADRs from CMF. Anthracyclines and Taxanes are now the standard treatment option for all breast cancer type as the ADR produced from this combination were lesser when compared to Anthracyclines alone [5]. Recent evidences showed improved efficacy when platinum compounds are added to Anthracycline-Taxane containing regimen for treating Triple Negative Breast Cancer (TNBC) [6]. Very recently, targeted therapy with Trastuzumab in HER-2 positive patients evidenced improved response [7].

All the chemotherapy drugs are with heavy potential to produce ADRs but severity and type of reaction varies among them. But safety data these regimens are limiting although established data available on individual drug only. This study aims to assess whether ADRs varies in patients with non-metastatic breast cancer when treated with 3 different chemotherapy regimens containing both Anthracycline and Taxane. The three regimens coming under the study are AC followed by Docetaxel (AC-T), AC followed by Docetaxel and carboplatin (AC-TCb) and AC followed by Docetaxel and Tastuzumab (AC-TH).

Methodology

Study design and participants

Prospective cohort study conducted at Department of Radiotherapy, Government Medical College, Kozhikode, India over a period of 8 months (January 2017-August 2017). All the patients with non-metastatic breast cancer who received chemotherapy with Doxorubicin, Cylophosphamide followed by Docetaxel or Doxorubicin, Cylophosphamide followed by Docetaxel and Carboplatin or Doxorubicin, Cyclophosphamide followed by Docetaxel and Trastuzumab as out-patients in day care chemotherapy ward or in patients under Dept. of Radiotherapy were included in the study. A minimum of 30 subjects in each study group were needed.

Inclusion criteria

- Subjects diagnosed with non-metastatic breast cancer prescribed with any of the chemotherapy regimen under study and atleast three cycles of scheduled chemotherapy remaining.
- Subjects treated either as neoadjuvant or adjuvant chemotherapy with 17-70 years of age.
- Both males and females are eligible for study.

Exclusion criteria

- Pregnant women.
- Prior chemotherapy or radiotherapy for any malignancy.
- Subjects with documented history of cardiac diseases contra-indicating Anthracyclines.
- Blind patients.
- Subjects with major psychiatric disorders like psychosis.
- Subjects with dementia or Alzheimer's disease.

Materials

- Case sheet of patients.
- Laboratory reports.
- NCI CTCAE Version 4.0.
- Cancer Care Ontario (CCO) drug monograph.

Study procedure: A prospective cohort study has been carried out in the Department of Radiotherapy, Govt. Medical College, Kozhikode for a period of 8 months. Subjects who satisfied eligibility criteria were enrolled for the study from January 2017 to April 2017 so that data can be obtained from all the subjects till the completion of the chemotherapy schedule. Demographic details of the subjects like age, sex, menstruation details as mentioned in Data Collection Form (DCF) were obtained during interview. Chemotherapy regimen was obtained from radiotherapy master file and individual case sheet. Routine blood investigation which is performed prior to each chemotherapy cycle was recorded from laboratory reports. All the collected data entered to Data Collection Form (DCF). Based on these data, each subject assigned subject number and followed them on each cycle of chemotherapy. Data on ADR were collected from each subject during interview and observed the reported ADR. Laboratory reports on 8th day after previous chemotherapy and on day of present chemotherapy also were collected. All possible ADRs on drugs under study were listed using Cancer care Ontario drug formulary. Reported ADRs were graded as per NCI CTCAE guideline. Details on ADR related hospitalization and medicines for the treatment were collected from discharge book from concerned department. All collected data was entered to Microsoft Excel 2010.

Statistical analysis

All entered data was analyzed using PASW statistics 18, 2009 version. Baseline characteristics were analyzed using frequency and percentage for qualitative data, mean and standard deviation for quantitative data. A statistical difference in the ADR among three regimens was analyzed using descriptives, cross tabs (chi-square test). The level of significance was set at 0.05. All p values less than 0.05 were considered as significant.

Results

Results of the present study are illustrated in **Tables 1-3.**

Table 1 Baseline measures.

	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (AC-T)	AC Followed by Docetaxel+Carboplatin (AC-TCb)	AC Followed by Docetaxel+Trastuzumab (AC-TH)	Total
Overall Subjects Analyzed [Units: Subjects]	84	52	54	190
Age [Units: Years] Mean (Standard Deviation)	49.14 ± 8.75	49.86 ± 9.30	48.74 ± 9.67	49.23 ± 9.132
Gender [Units: Subjects]				
Female	84	52	54	190
Male	0	0	0	0
Menstrual status [Units: Subjects]				
Pre-menopausal	36	17	25	78
Post-menopausal	48	35	29	112

Table 2 Serious Adverse Events (SAE).

	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (AC-T)	AC Followed by Docetaxel+Carboplatin (AC-TCb)	AC Followed by Docetaxel+Trastuzumab (AC-TH)
Total, SAE # Subjects affected/ at risk (%)	38/84 (45.23%)	21/52 (40.38%)	14/54 (25.92%)
Blood and lymphatic system disorders			
Anemia # Subjects affected/ at risk (%)	3/84 (3.6%)	1/52 (1.9%)	2/54 (3.7%)
Febrile neutropenia # Subjects affected/ at risk (%)	9/84 (10.7%)	5/52 (9.6%)	4/54 (7.4%)
Neutropenia # Subjects affected/ at risk (%)	19/84 (22.62%)	15/52 (28.85%)	11/54 (20.37%)
Gastro-Intestinal disorders			
Diarrhea # Subjects affected/ at risk (%)	0/84 (0.00%)	1/52 (1.9%)	0/54 (0.00%)
Mucositis # Subjects affected/ at risk (%)	1/84 (1.2%)	1/52 (1.9%)	0/54 (0.00%)
Vomiting # Subjects affected/ at risk (%)	1/84 (1.2%)	1/52 (1.9%)	0/54 (0.00%)
Constipation # Subjects affected/ at risk (%)	0/84 (0.00%)	1/52 (1.9%)	0/54 (0.00%)
Dermatological reactions			
Cutaneous reactions # Subjects affected/ at risk (%)	8/84 (9.5%)	3/52 (5.8%)	2/54 (3.7%)
Hand-foot syndrome # Subjects affected/ at risk (%)	3/84 (3.60%)	1/52 (1.9%)	0/54 (0.00%)
Musculo-skeletal reactions			
Myalgia # Subjects affected/ at risk (%)	1/84 (1.2%)	0/52 (0.00%)	0/54 (0.00%)
Psychological reactions			
Insomnia # Subjects affected/ at risk (%)	14/84 (16.67%)	8/52 (15.38%)	7/54 (12.96%)
Auditory reactions			
Hearing impaired # Subjects affected/ at risk (%)	1/84 (1.2%)	0/52 (0.00%)	0/54 (0.00%)

Table 3 Other adverse events.

	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (AC-T)	AC Followed by Docetaxel+Carboplatin (AC-TCb)	AC Followed by Docetaxel+Trastuzumab (AC-TH)

Total, Other (not including serious) Adverse Events # Subjects affected/ at risk (%)	84/84 (100%)	52/52 (100%)	54/54 (100%)
Blood and lymphatic system disorders			
Anemia # Subjects affected/ at risk (%)	0/84 (0.00%)	0/52 (0.00%)	0/54 (0.00%)
Febrile neutropenia # Subjects affected/ at risk (%)	0/84 (0.00%)	0/52 (0.00%)	0/54 (0.00%)
Neutropenia # Subjects affected/ at risk (%)	21/84 (25.0%)	9/52 (17.30%)	13/54 (24.07%)
Thrombocytopenia # Subjects affected/ at risk (%)	1/84 (1.2%)	2/52 (3.8%)	1/54 (1.9%)
Gastro-Intestinal disorders			
Diarrhea # Subjects affected/ at risk (%)	41/84 (48.80%)	30/52 (67.30%)	26/54 (48.14%)
Mucositis # Subjects affected/ at risk (%)	47/84 (56.0%)	21/52 (40.4%)	32/54 (59.2%)
Vomiting # Subjects affected/ at risk (%)	35/84 (41.67%)	34/52 (65.38%)	29/54 (53.70%)
Constipation # Subjects affected/ at risk (%)	50/84 (59.5%)	26/52 (50.0%)	32/54 (59.2%)
Anorexia # Subjects affected/ at risk (%)	52/84 (62.0%)	35/52 (67.3%)	35/54 (64.8%)
Nausea # Subjects affected/ at risk (%)	42/84 (50.0%)	29/52 (55.8%)	23/54 (42.6%)
Dermatological reactions			
Buccal hyper-pigmentation # Subjects affected/ at risk (%)	64/84 (76.19%)	46/52 (88.46%)	49/54 (90.74%)
Hand-foot syndrome # Subjects affected/ at risk (%)	1/84 (1.2%)	1/52 (1.9%)	0/54 (0.00%)
Cutaneous reactions # Subjects affected/ at risk (%)	44/84 (52.4%)	19/52 (36.5%)	8/54 (14.8%)

Alopecia **# Subjects affected/ at risk (%)**	84/84 (100%)	52/52 (100%)	54/54 (100%)
Skin hyper-pigmentation **# Subjects affected/ at risk (%)**	54/84 (64.3%)	37/52 (71.1%)	41/54 (75.9%)
Nail discoloration **# Subjects affected/ at risk (%)**	81/84 (96.4%)	46/52 (88.4%)	48/54 (88.9%)
Musculo-skeletal reactions			
Myalgia **# Subjects affected/ at risk (%)**	24/84 (28.57%)	20/52 (38.46%)	17/54 (31.48%)
Psychological reactions			
Insomnia **# Subjects affected/ at risk (%)**	22/84 (26.19%)	11/52 (21.15%)	13/54 (24.07%)
Auditory reactions			
Hearing impaired **# Subjects affected/ at risk (%)**	0/84 (0.00%)	1/52 (1.9%)	0/54 (0.00%)
Cardio-vascular reactions			
Arrhythmia **# Subjects affected/ at risk (%)**	0/84 (0.00%)	0/52 (0.00%)	1/54 (1.9%)
Hypertension **# Subjects affected/ at risk (%)**	1/84 (1.2%)	1/52 (1.9%)	0/54 (0.00%)
Hypotension **# Subjects affected/ at risk (%)**	2/84 (2.4%)	0/52 (0.00%)	1/54 (1.9%)
Ophthalmological reactions			
Watering eyes **# Subjects affected/ at risk (%)**	15/84 (17.9%)	13/52 (25.0%)	11/54 (20.4%)
Blurred vision **# Subjects affected/ at risk (%)**	3/84 (3.6%)	1/52 (1.9%)	1/54 (1.9%)
Administration site reactions			
Injection site reactions **# Subjects affected/ at risk (%)**	2/84 (2.4%)	8/52 (15.4%)	3/54 (5.6%)
Pain at injection site **# Subjects affected/ at risk (%)**	0/84 (0.00%)	6/52 (11.5%)	8/54 (14.8%)

Injection site edema **# Subjects affected/ at risk (%)**	16/84 (19.0%)	16/52 (30.8%)	13/54 (24.1%)
General reactions			
Fever and chills **# Subjects affected/ at risk (%)**	18/84 (21.4%)	18/52 (34.6%)	24/54 (44.4%)
Fatigue **# Subjects affected/ at risk (%)**	34/84 (40.5%)	31/52 (59.6%)	44/54 (81.5%)
General edema **# Subjects affected/ at risk (%)**	26/84 (31.0%)	21/52 (40.4%)	28/54 (51.9%)
Phlebitis infective **# Subjects affected/ at risk (%)**	25/84 (29.8%)	11/52 (21.2%)	17/54 (31.5%)
Respiratory reactions			
Cough **# Subjects affected/ at risk (%)**	28/84 (33.3%)	17/52 (32.7%)	15/54 (27.8%)
Upper Respiratory Tract Infection **# Subjects affected/ at risk (%)**	13/84 (15.5%)	15/52 (28.8%)	17/54 (31.5%)
Neurological reactions			
Dysgeusia **# Subjects affected/ at risk (%)**	38/84 (45.2%)	23/52 (44.2%)	21/54 (38.9%)
Vertigo **# Subjects affected/ at risk (%)**	11/84 (13.1%)	5/52 (9.6%)	4/54 (7.4%)
Headache **# Subjects affected/ at risk (%)**	26/84 (31.0%)	15/52 (28.8%)	25/54 (46.3%)
Peripheral neuropathy **# Subjects affected/ at risk (%)**	16/84 (19.0%)	6/52 (11.5%)	10/54 (18.5%)
Reproductive system disorders			
Amenorrhea **# Subjects affected/ at risk (%)**	25/36 (69.4%)	13/17 (76.5%)	19/25 (76.0%)
Irregular menstruation **# Subjects affected/ at risk (%)**	18/36 (50.0%)	5/17 (29.4%)	11/25 (39.7%)

Discussion

Baseline characteristics of the subjects

Incidence of breast cancer was high in patients under the age group of 41-50 and majority of the population aged between 41-60 from all the groups. All the subjects were female. Breast cancer is the most common malignancy amongst women in both developed and developing countries [8]. Martin et al. pointed

out that, in females, breast cancer accounts for about 22% which is more than twice the prevalence of cancer at any other site [9]. Mean age was 49.14 years for AC-T, 49.86 for AC-TCb and 48.74 for AC-TH. The results were analogous with CIRG [10] trial where mean age was 48.7 for AC-TH. All the enrolled subjects were female in CIRG trial also. Majority of the population from all the study groups were post-menopausal. This result correlates with study conducted by Yuan and Xu [11]. Incidence of breast cancer was higher at the age 41-60 as most of the female reaches menopause at this age. Study correlates to the fact that risk for breast cancer increases as age progresses.

Adverse drug reactions

All the reported ADRs were categorized under thirteen SOC. General disorders were significant among all SOCs. ADRs were graded as per NCI CTCAE criteria version 4.03. All the subjects under study experienced any of the ADR. Dermatological reactions were present in all enrolled subjects. But in CIRG trial 99.9% from AC-T and 100% from AC-TH were exposed to ADRs.

Dermatological reactions: Severe forms of cutaneous reactions with localized eruptions from face, legs, hands and breast. Alopecia present for all the subjects was Grade 2. Alopecia was common and appeared early (days to week) in this study and the results coincide with reports from Cancer Care Ontario drug formulary [12] (alopecia reported for all the drugs under study). But CIRG result shows it was not present in all trial subjects. Palmar-plantar erythrodysesthesia syndrome commonly called as hand-foot syndrome was rare and presented in severe forms for majority cases. Each subject from both AC-T and AC-TCb had Grade 2 form. Grade 3 type was seen in 3 subjects from AC-T and 1 from AC-TCb. Results correlates with reports from CCO drug formulary. Skin hyperpigmentation was presented early in all subjects and was Grade 1 type. Hyperpigmentation were commonly seen on hands although it is appeared on other parts of the body like face or all over the body. Skin hyperpigmentation also not affected much in trial subjects although reported highly from our subjects. Higher incidence was reported from AC-TH group but in AC-T subjects from the trial.

All subjects with nail discoloration belong to Grade 1 category. A severe form of nail disorder onychylosis was present in 2 subjects from AC-T. Nail disorders were higher in AC-T group. Similar results obtained from the trial also. Severe exfoliative cutaneous reactions presented were higher in AC-T group and the results were similar from the CIRG trial. The subjects affected with cutaneous reactions among the groups were far higher than that from trial.

Gastrointestinal reactions: Majority of the reported gastro-intestinal ADRs were mild among the groups. For anorexia and nausea, no severe reactions observed and the trial results were not similar. Anorexia, constipation and diarrhea were seen higher in percentage than from trial in all study group but nausea was not that much seen in clinical trials in the study subjects.

Each subject from AC-T and AC-TCb had Grade 4 vomiting. Grade 1 form was seen in 26 subjects from AC-T, 18 from AC-TCb and 21 from AC-TH; Grade 2 type was present in 9 from AC-T, 16 from AC-TCb, 8 from AC-TH. Vomiting was statistically significant and was higher for AC-TCb and a similar result obtained from CCO data. Subjects suffered from vomiting were lesser than from the trials and CCO reports. Severe vomiting was present only in AC-T group although it was present in all the groups from trial. Vomiting appeared as immediate ADR as similar in CCO reports. All the subjects with anorexia belong to Grade 1 type, mild although severe forms reported from CIRG trial. More subjects from this study suffered from anorexia than from trial. Anorexia was reported as ADR for all drugs except Trastuzumab from CCO drug monograph. Constipation was less in AC-TCb group when compared to others. Out of 27 subjects 23 had Grade 1 and 3 had Grade 2. One subject had Grade 3. For AC-T, 50 subjects (59.5%) had constipation, of which 41 had Grade 1 and 9 had Grade 2. 32 subjects (59.3%) from AC-TH had constipation, 25 with Grade 1 and 7 with Grade 2. As per CCO, constipation was reported as early ADR and present for all the drugs in the study. AC-TH group was more affected with mucositis. Grade 1 was seen in 24 subjects and 8 had Grade 2. From AC-T, 36 subjects had Grade 1 and 11 had Grade 2. From AC-TCb 14 had Grade 1 and 7 had Grade 2. Single subject each from AC-T and AC-TCb had severe form of mucositis, Grade 4. Mucositis appeared as early ADR as similar to CCO report. Severe reactions were lesser than from the same. Out of 41 subjects from AC-T with diarrhea, 25 had Grade 1 and 6 had Grade 2. From AC-TCb, 23 subjects had Grade 1 and 7 had Grade 2 and one suffered from Grade 3 type. From AC-TH 21 had Grade 1 and 5 had Grade 2. Diarrhea was present as early ADR. It was present in less number of AC-TH subjects than from CCO reports. Nausea was present in 55.8% of AC-TCb subjects. All subjects had Grade 1 or Grade 2 type. From AC-T 20 subjects had Grade 1 nausea and 22 had Grade 2. Grade 1 nausea was seen in 18 subjects from AC-TCb group and Grade 2 for 11 subjects. For AC-TH 14 had Grade 1 and 9 had Grade 2. Nausea was present in lesser population than reported in CCO. All reported nausea as early ADR. Severe form was present in CIRG trial subjects but not evidence in our studies.

Hematological reactions: All the recorded anemia cases were severe, Grade 3 or 4. Grade 3 anemia was seen in 2 subjects from both AC-T and AC-TH and one from AC-TCb. Grade 4 present for 1 subject from AC-T. All anemia cases were treated with PRBC transfusion. Subjects with decreased platelet count came under Grade 1 type. 1 subject from AC-TCb had purpura. Thrombopoeitic agents were prescribed for all suffered subjects. Subjects with febrile neutropenia were graded under 3 or 4. 1 from AC-T had Grade 4 and all others with Grade 3. Neutropenia was the common hematological ADR in the all groups. 4 subjects from AC-T 2 from AC-TCb 1 from AC-TCH had Grade 1. 17 from AC-T, 7 from AC-TCb and 12 from AC-TH had Grade 2. 15 from AC-T, 11 from AC-TCb and 8 from AC-TH had Grade 3. 4 from AC-T, 1 from AC-TCb and 3 from AC-TH had Grade 4. Granulocyte Colony Stimulating Factor was prescribed for all the cases. IV and oral antibiotics were given based on severity.

ADR from blood and lymphatic system were less than that in the trial and CCO reports. Serious ADR were anemia, febrile neutropenia and neutropenia. In AC-T severe anemia was present in 0.10% and in AC-TH it was 0.73% from trial. Results obtained here were higher than that from the CIRG trial. The result was contradictory with Geparsixto GBG 66 trial [13] as it stated

that incidence of severe hematological reactions were high in carboplatin containing group. Results from study conducted by Coudert and Largillier [14] showed that Grade 3/4 neutropenia and febrile neutropenia were uncommon (2%) and was not coinciding with this study. But severe reactions were negligible when CCO reports were compared. Thrombocytopenia observed was not severe. Myelosuppression were 55% for carboplatin alone and severe type of myelosuppression may account up to 7.5% in subjects treated with Docetaxel. Serious neutropenia observed in this study were found to be higher than that from the trial (2.06% for AC-T and 2.09% for AC-TH). Febrile neutropenia was present for 19.1% subjects in study conducted by Redana et al. [15].

Cardiovascular reactions: All the cardio vascular reactions reported were mild, Grade 2. Obtained results were less than that from CCO reports. Study was in line with studies conducted by Pierga et al. [16] as well as Coudert as no severe cardiotoxicity reported from their study. Severe types were reported from CIRG trial as it was not in this study.

Ophthalmological reactions: All subjects with watering eyes were grouped under Grade 1. From AC-TCb 1 had blurred vision of Grade 1 type and remaining Grade 2 type from other groups.

Watering eyes were higher in carboplatin containing group from our study followed by Trastuzumab containing group whereas later affected more in the trial subjects. Subjects in our study were less affected with visual disturbances than reports from CCO.

Administration site reactions: All the injection site reactions were Grade 2 and phlebitis was present for all of them. From AC-TCb 3 subjects, 5 from AC-TH had Grade 1 pain and remaining had Grade 2. From AC-T 12 Subjects, 13 from AC-TCb, 12 from AC-TH had Grade 1 edema and remaining had Grade 2. CCO reports a lesser amount of injection site reactions than our study results. Injection site reaction was common in carboplatin containing group and similar result obtained from trial also. Subjects in our study group were not affected with pain at the site of administration that much from trial subjects.

General reactions: All the fever reported were Grade 1 type, was higher in AC-TH group. From AC-TH 81.5% of subject suffered with fatigue, 9 had Grade 2 and 35 had Grade 1. From AC-TCb 15 subjects and 16 from AC-T had Grade 2 fatigue, remaining with Grade 1. Edema was reported from 51.9% of AC-TH subjects. Upper and lower limbs and face were the common sites where edema was present. All phlebitis infective cases were Grade 2 type. Subjects from AC-TH were affected more with edema, fever and chills and similar results obtained from CIRG trial also.

Musculoskeletal reaction: From AC-T 9 subjects, 8 from AC-TCb and 6 from AC-TH suffered from Grade 1 myalgia and 1 subject from AC-T had Grade 3 and remaining belonged to Grade 2.

Mylagia was affected more for subjects taking carboplatin followed by Trastuzumab whereas the later affected more in the CIRG trial. Although myalgia was present as early ADR in this study subjects it was reported as delayed ADR from CCO reports.

Neurological reactions: Although documented subjects belongs to Grade 1 and 2 type dysgeusia, majority contributed later class and 26 from AC-T, 13 from both AC-TCb and AC-TH came under this category. All remaining belongs to Grade 1. From AC-T 11 subjects, 2 from AC-TCb and 3 from AC-TH belongs to Grade 1. The remaining contributes Grade 2. From AC-T 16 subjects, 9 from AC-TCb and 14 from AC-TH had Grade 1 head ache. Grade 2 was present for the remaining subjects. All the subjects suffering from peripheral neuropathy came under Grade 1.

All the reported neurological reactions were mild but severe reactions reported from CIRG trials. Peripheral neuropathy and vertigo was higher among AC-T group. But AC-TH was affected more with neuropathy from trial. Peripheral neuropathy was observed in this study in less percentage than from CCO reports. Results from Vriens et al. [17] study show peripheral neuropathy in 5.0% subjects.

Respiratory reactions: Cough was seen in 33.3% subjects from AC-T, of which 15 had Grade 1 and 13 had Grade 2. From AC-TCb, 10 subjects had cough Grade 1 and 7 had Grade 2. From AC-TH, 11 subjects presented with Grade 1 and 4 with Grade 2 cough. Respiratory tract infections distressed 31.5% subjects from AC-TH.

Cough was higher among AC-T from our study whereas both AC-T and AC-TH affected equally from trial. Subjects affected with upper respiratory tract infection were more in AC-TH in this study and correlates with the CIRG trial. Severe infections were reported from trial and were not from this study.

Psychological reaction: Insomnia Grade 3 was present in 14 subjects from AC-T, 8 from AC-TCb, 7 from AC-TH. From AC-T 10 subjects, 7 from AC-TCb and 8 from AC-TH had Grade 2 and remaining had Grade 1. Insomnia was more distressing ADR among AC-T and severe type were present among study subjects. Higher number of patients suffered by sleep was from AC-TH from the CIRG trial and no severe type reported from study groups.

Auditory reaction: From AC-TCb 1 subject and 1 from AC-T had hearing impairment during chemotherapy, Grade 2 and Grade 4 respectively. Hearing impairment may be presented as late effects of chemotherapy.

Reproductive system disorders: Observed ADRs under reproductive system was reported from premenopausal subjects only. All the subjects with irregular menstruation belong to Grade 1 only. Further follow up may help to find whether those turned to higher Grades. Similar follow up needed for subjects with amenorrhea also needed. Regular follow up may help to distinguish between menopause and amenorrhea as chemotherapy induced amenorrhea in early ages is reversible within six months.

All the enrolled subjects successfully completed the chemotherapy schedule. In study by Yuan and Xu, 2 subjects from carboplatin group discontinued the treatment due to bone marrow suppression. In study by Redana [15], 2 patients died due to toxicity from treatment. None of the ADR resulted in withdrawal of the subjects from chemotherapy regimen. Dose reduction was performed for 2 subjects from AC-T as one had recurrent neutropenia and other with severe cutaneous reactions

with exfoliation from breast. Dechallenge was carried out for one subject from AC-T with anaphylaxis and re-challenged after ten minutes and the subject had no further complaints. Medications after chemotherapy highly helped to reduce ADRs. Absence of nephrological and hepatic toxicity from the obtained results leads to acceptance of therapy if efficacy results were proven.

Limitations of this study

Delayed effects of many of the drugs cannot be taken in to account to get the complete picture on ADRs as the time limits the study. Hepatic, renal, neurological and cardio-toxicity mainly occurs from months to years after completing the treatment. If regular cardiac check-up after each cycle of chemotherapy were recommended, a good and clear picture on cardio toxicity may be obtained as report on palpitation or shortness of breath cannot merely state as cardio toxicity. Financial difficulty for subjects for Echocardiography can be ignored if the benefit for early detection can be considered. Also a good follow up at third, sixth and twelfth month after completing treatment will help to obtain the details on delayed ADRs.

Conclusion

In the current scenario of cancer chemotherapy in India, only a least emphasize is given for its adverse effects management. As Anthracycline and Taxane based regimen is the core treatment method for BC in the present situation and addition of Trastuzumab or carboplatin had proven beneficial to subtypes. From our study it is clear that, ADRs were not aggravated when Taxanes used in combination. All the subjects receiving any of the regimens under study were well tolerated to treatment. Majority of the ADRs were mild. ADRS experienced were comparable with phase III trial results. It is an interesting fact that some of them appeared in lower units than from the same. Many of the ADRs were recovered after supportive treatment.

Chemotherapeutic drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells. However, early detection of drug toxicity helps to modify the doses or the drug regimen to minimize toxic effects. More conclusive results can be obtained when the similar study conducted for longer duration of time with large sample size.

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