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A Prospective Observational Study of Cardiac Safety, Adverse Drug Reactions And Its Management of Adriamycin + Cyclophosphamide Regimen In Breast Cancer Patients

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Abstract *— This study aims to evaluate cardiac safety, adverse drug reactions, and its management of the Adriamycin+Cyclophosphamide regimen in breast cancer patients. 33 female breast cancer patients enrolled in the study and assigned to the treatment with Adriamycin, Cyclophosphamide, followed by monitoring the cardiac safety analysis, A.D.R., and its management assessed. This study observes that the main way to prevent cardiac toxicity is to limit the cumulative dose of drugs that damage the heart, especially the anthracyclines. There is a defined amount of doxorubicin that can be given with a lesser risk of complications. If the total dose of doxorubicin is less than 550mg/m2, there is a 20 % chance of cardiac toxicity. If the full dose of doxorubicin is between 560-1155mg/m2, the risk increases to 30%.*

Keywords — *Adriamycin, Doxorubicin, Cyclophosphamide, A.C. regimen, breast cancer*

I. INTRODUCTION

In this new era of modern lifestyle, cancer incidence is rapidly increasing worldwide and leads to an increase in death rate. Among the prevalence of cancer, breast cancer is the 2nd leading cause of mortality among women. For breast cancer, it is necessary to design an effective regimen to improve cancer patients' survival rates.

The cardiovascular side effects of cancer treatments remain a challenge in oncologic care. Patients with cancer and cancer survivors have an increased risk of adverse cardiovascular outcomes, including left ventricular (LV) dysfunction, heart failure (H.F.), and acute coronary events. A.C. regimen is widely used as an effective therapy for breast cancer. However, the incidence of cardiac side effects is very common; thus, we sought to explore the cardiac and other side effects of the A.C. regimen management.

During the year 2017-2018, 132 breast cancer cases alone reported 497 cancer cases (26.55%) in Erode Cancer Centre, in which most patients are diagnosed with primary breast cancer (stage 2 and 3).

A.C. regimen chemotherapy can treat primary breast cancer that hasn't spread beyond the breast or the lymph nodes under the arm. It takes its name from the initials of these drugs:

- Doxorubicin (also known as Adriamycin)
- Cyclophosphamide.

A.C. regimen was approved for medical use in the United States. One of the W.H.O. lists of essential medicine was effective and safe medicine needed in a health system. A.C. regimen chemotherapy works by stopping the cancer cells from dividing and multiplying, which blocks cancer growth. A.C. regimen chemotherapy is a systemic treatment, which means it affects cells throughout the body.

II. METHODOLOGY

33 female breast cancer patients enrolled in the study and assigned to the treatment with Adriamycin, Cyclophosphamide, followed by monitoring the cardiac safety analysis, A.D.R., and its management assessed.

Source of data: Patient Case Report Form.
Study location: Erode Cancer Centre Hospital
Duration: Feb 2019 –Jul 2019
Type of Study: Prospective observational study
Population : 33 patients

A. Inclusion Criteria:

- Female patient Age from 18yrs to 65 yrs.
- All patients must have histological confirmed and newly diagnosed breast cancer.
- No prior chemotherapy or radiotherapy is allowed.

- Adequate hepatic, renal, hematopoietic, and cardiac function.
- At least one measurable lesion according to response evaluation criteria in solid tumours.

B. Exclusion Criteria:

- Pregnant and lactating women.
- The patient who received hormonal, chemotherapy, radiotherapy
- The patient has a history of cancer other than in situ uterine cervix cancer or non-melanotic skin cancer.
- Patient with ongoing or active infections
- The patient was receiving chronic antiplatelet or anticoagulant therapy.
- Known case of Hypertension, H.I.V. infection, or diabetes.

C. Study Phase - I:

- Literature survey
- Protocol preparation
- Approval from the Hospital Ethical Committee

D. Study Phase - II:

- Developing the criteria for selected topic based on Eastern Cooperative Oncology Group and ICH-GCP guidelines
- Preparation of data collection form
- Data collection based upon inclusion and exclusion criteria
- Data collection from wards of oncology Department

E. Study Phase - III:

- Data analysis
- Clinical pharmacist's intervention
- Result interpretation

III. RESULTS

TABLE NO.1
Age-wise distribution of study population

S.L. No	AGE GROUP (years)	NO OF PATIENTS (n=33)	PERCENTAGE
1	20-30	0	0%
2	31-40	7	21%
3	41-50	9	26%
4	51-60	17	50%
5	61-70	1	3%

TABLE NO.2
Morphological categorization of the study population

MORPHOLOGY	NO: PATIENTS (n=33)	PERCENTAGE
Ductal and lobular	1	3%
Ductal	8	24%
Invasive ductal	18	55%
Duct carcinoma	6	18%

TABLE NO.3
Stage on diagnosis

STAGES	NO OF PATIENTS (n=33)	PERCENTAGE
STAGE 1	0	0%
STAGE 2	15	46%
STAGE 3	18	54%
STAGE 4	0	0%

TABLE NO.4
Blood pressure cehanges in cycle 1 (according to WHO)

CHANC	MILD		MODERATE		SEVERE	
	NO OF PATIENTS (n=33)	PERCENTAGE	NO OF PATIENTS (n=33)	PERCENTAGE	NO OF PATIENTS (n=33)	PERCENTAGE
HYPERTENSION	14	42%	5	15%	0	0%

HYPERTENSION (mm/Hg):
MILD (140/90- 159/99)
MODERATE (160/100-179/109)
SEVERE (>180/110)

TABLE NO.5
Blood pressure changes in cycle 2 (according to WHO)

CHAN	MILD		MODERATE		SEVERE	
	NO OF PATIENTS (n=33)	PERCENTAGE	NO OF PATIENTS (n=33)	PERCENTAGE	NO OF PATIENTS (n=33)	PERCENTAGE
HYPERTENSION	20	61%	4	12%	0	0%

TABLE NO.6
Blood pressure changes in cycle3 (according to WHO).

BP CHANGES	HYPERTENSION			HYPOTENSION
	MILD	MODERATE	SEVERE	
NO OF PATIENTS (n=33) (%)	25 (75%)	0 (0%)	0 (0%)	2 (6%)

TABLE NO.7
Blood pressure changes in cycle 4 (according to WHO).

H A N	HYPERTENSION			HYPOTENSION
	MILD	MODERATE	SEVERE	
NO OF PATIENTS (n=33) (%)	10 (30%)	5 (15%)	0 (0%)	1 (3%)

TABLE NO.8
LVEF grading in patients from echo (according to the American college of cardiology foundation)

LVEF CHANGES	NO OF PATIENTS (n=33)	%
NO CHANGE	24	72%
MILD	7	22%
MODERATE	1	3%
SEVERE	1	3%

Normal = LVEF 50% to 70% (midpoint 60%).
Mild dysfunction = LVEF 40% to 49% (midpoint 45%).
Moderate dysfunction = LVEF 30% to 39% (midpoint 35%).
Severe dysfunction = LVEF less than 30%

TABLE NO.9
General A.D.R. was reported in all study subjects.

ADR	NO OF PATIENTS (n=33)	%
Alopecia	33	100%
Burning micturition	15	46%
Fatigue	17	53%
Hematuria	5	15%
Tissue extravasation	23	69%
Sore throat	13	38%
Swelling of face and lips	10	31%
Joint pain	15	46%
Lightheadedness and dizziness	30	92%
Nail and skin discoloration	23	69%
Impaired vision	1	3%

TABLE NO.10
General A.D.R. reported in all 4 cycles.

GI EFFECTS	NO OF PATIENTS (n=33)	%
FATIGUE	17	53%
SORE THROAT	13	38%
LIGHT HEADLESS	30	92%

TABLE NO.11
General A.D.R. reported in second and third cycles

GI EFFECT	NO OF PATIENTS (n=33)	PERCENTAGE
ALOPECIA	33	100%
TISSUE EXTRAVASATION	16	48%
HEMATURIA	5	15%
BURNING MICTURITION	12	36%
SWELLING OF FACE AND LIPS	4	12%
JOINT PAIN	7	21%
NAIL AND SKIN DISCOLORATION	13	38%

TABLE NO.12
General A.D.R. reported in second and fourth cycles

GI EFFECT	NO OF PATIENTS (n=33)	PERCENTAGE
TISSUE EXTRAVASATION	7	21%
BURNING MICTURITION	3	9%
SWELLING OF FACE AND LIPS	6	18%
IMPAIRED VISION	1	3%
JOINT PAIN	8	24%
NAIL AND SKIN DISCOLORATION	10	31%

TABLE NO.13
Gastrointestinal A.D.R. reported in all study subjects

GI EFFECTS	NO. OF PATIENTS (n=33)	PERCENTAGE
BURNING SENSATION	15	46%
NAUSEA VOMITING	33	100%
DIARRHOEA	13	38%
ORAL MUCOSITIS	15	46%
LOSS OF APPETITE	15	46%
CONSTIPATION	5	15%
BLACK STOOLS	15	46%

TABLE NO.14
Gastrointestinal A.D.R. reported in all four cycles

GI EFFECTS	NO OF PATIENTS (n=33)	PERCENTAGE
NAUSEA AND VOMITING	33	100%
LOSS OF APPETITE	15	46%
BURNING SENSATION	15	46%

TABLE NO.15
Gastrointestinal A.D.R. reported in 2 and 3 cycles

GI EFFECT	NO OF PATIENTS (n=33)	PERCENTAGE
DIARRHOEA	8	24%
CONSTIPATION	5	15%
BLACK STOOLS	11	33%
ORAL MUCOSITIS	5	15%

TABLE NO.16
Gastrointestinal A.D.R. reported in the fourth Cycle

GI EFFECT	NO OF PATIENTS (n=33)	PERCENTAGE
DIARRHOEA	5	15%
BLACK STOOLS	4	12%
ORAL MUCOSITIS	10	30%

TABLE NO.17
Hematological changes after cycle-1 (According to CTCAE version 5.0)

ADR	MILD		MODERATE		SEVERE	
	n	%	n	%	n	%
ANEMIA	8	23 %	3	8%	0	0%
LEUKO PENIA	0	0%	0	0%	0	0%
THROMBO CYTOPENIA	0	0%	0	0%	0	0%

ANAEMIA (g/dl): mild (10-10.9) moderate (7.0-9.9) severe (< 7.0 g/dl)
LEUKOPENIA (mm3): mild (LLN- < 3000) moderate (< 3000-2000) severe (< 2000)
THROMOBOCYTOPENIA (mm3): mild (<LLN-75000) moderate (< 75000-50000) severe (< 50000)

TABLE NO.18
Hematological changes after cycle-2

ADR	MILD		MODERATE		SEVERE	
	n	%	n	%	n	%
ANEMIA	8	23%	3	8%	0	0%
LEUKO PENIA	0	0%	0	0%	0	0%
THROMBO CYTOPENIA	0	0%	0	0%	0	0%

TABLE NO.19
Hematological changes after cycle-3

ADR	MILD		MODERATE		SEVERE	
	n	%	n	%	n	%
ANEMIA	8	23%	3	8%	0	0 %
LEUKO PENIA	0	0%	0	0%	0	0 %
THROMBO CYTOPENIA	0	0%	0	0%	0	0 %

TABLE NO.20
Hematological changes after cycle-4 (according to CTCAE Version 5.0)

ADR	MILD		MODERATE		SEVERE	
	n	%	n	%	n	%
ANEMIA	12	38%	9	24%	0	0 %
LEUKO PENIA	8	23%	0	0%	0	0 %
THROMBO CYTOPENIA	9	24%	0	0%	0	0 %

TABLE NO. 21
Gastrointestinal A.D.R. management

ADVERSE EFFECTS	n	%	MANAGEMENT OF ADR
BURNING SENSATION	15	46%	Syp Antacid (Aluminum and magnesium) 5 ml
NAUSEA VOMITING	33	100 %	Tab ondansetron 4 mg
DIARRHOEA	13	38%	Tab. Metronidazole 400mg
ORAL MUCOSITIS	15	46%	Cryotherapy Mouth gargle
LOSS OF APPETITE	15	46%	-
CONSTIPATION	5	15%	Syp. Cremaffin 5ml
BLACK STOOLS	15	46%	-

TABLE NO.22
General A.D.R. management

ADVERSE EFFECTS	n	%	MANAGEMENT OF ADR
ALOPECIA	33	100%	Caps or wigs
BURNING MICTURITION	15	46%	Syrup potassium citrate 1100mg+ magnesium citrate 375mg+ hydrochloride 20mg
FATIGUE	17	53%	Diet modifications, iv hydration
HEMATURIA	5	15%	Drink about more fluid daily
TISSUE EXTRAVASATION	23	69%	-
SORE THROAT	13	38%	Saline gargle
SWELLING OF FACE AND LIPS	10	31%	-
IMPAIRED VISION	1	3%	-
JOINT PAIN	15	46%	Analgesics(topical), Tab paracetamol 650mg
LIGHTHEADEDNESS AND DIZZINESS	30	92%	Tab paracetamol 650 mg
NAIL AND SKIN DISCOLOURATION	23	69%	-

IV. DISCUSSION

In our study, the age distribution of A.D.R. incidence was found higher in the age group of 51 –60 years (50%), whereas it was found lower between the ages 61-70 years(3%). So the study concluded that cardiac changes and other A.D.R. were mainly occurred between the age group of 51-60 years (50%), as shown in Table:1 Adverse drug reaction mainly occurs in both ages 51-60 years (50%)and 41-50 (26%).

In morphological characterization, it shows that most breast cancer is invasive ductal carcinoma, that is, 18 patients (55%) out of 33 patients. Then ductal carcinoma in 8 patients (24%). Duct carcinoma in 6 patients (18%). And both ductal and lobular in 1 patient (3%) (Table: 2)

Table: 4 showed breast cancer stage-wise distribution of study subjects that more patients were stage 3, 18 patients during initial diagnosis (54%)]. Most cardiac changes occur in stage 3 patients. There are no patients in stage 1 and stage 4 initial diagnoses because they have deviated from our inclusion criteria.

Blood pressure changes in cycle 1, mild Hypertension was observed in 14 patients (42%) and moderate in 5 patients (15%). No severe hypertension was found in the first Cycle, and hypotension was not observed (Table: 5).

Blood pressure changes in Cycle 2showed in Table.6. Mild Hypertension was observed in 20patients (61%) after chemotherapy and moderate in 4 patients (12%). No severe hypertension and hypotension were found in the 2nd Cycle. Hypertension was mainly observed only after chemotherapy. Before chemotherapy, the patient blood pressure was normal.

Table: 7 shows that the blood pressure changes in cycle 3; mild Hypertension was observed in 25patients (75%) after the chemotherapy, and no moderate and severe hypertension was found. Hypotension was also observed for 2 patients (6%) after chemotherapy, 2 patients were observed with hypotension and preferred ECHO for cardiac analysis.

As shown in Table:8Blood pressure changes in cycle 4, mild Hypertension was observed in 10patients (30%) after the chemotherapy and moderate was observed in 5 patients (15%), and no severe hypertension was found in the 3rd Cycle, whereas hypotension will also be observed for 1 patient (3%) after chemotherapy.

Cardiac safety from the evaluation of LVEF grading in patients from ECHO shows a severe change in LVEF in 1 patient (3%) and moderate change in 1 patient (3%), which coincides with the finding of a study conducted by Erratumin et al., (2005) and Perez E.A. et al., (2010) concluded that the standard A.C. chemotherapy is associated with a frequent decrease in LVEF which are noted when measured 3 weeks after completion of 4 cycles. The mild change was found in 7 patients (22%), and no changes were observed in 24 patients (72%) (Table: 9). the patient who gets a mild and moderate change in LVEF will produce hypotension in the 3rd and 4th Cycles.

So it is found out that the A.C. regimen induces mild and moderate Hypertension after all 4 cycles, but hypotension will occur only at cycles 3 and 4. So ECHO and E.C.G. were preferred for such patients to evaluate

cardiac safety. This report concluded that only 1 patient was severe, 7 Patients with mild, and 1 patient with moderate changes.

General A.D.R. shown in Table.10 the study reported in all study subjects was alopecia in 33 patients (100%) light headiness and dizziness in 30 patients(92%) nail and skin discoloration and tissue extravasations in 23 patients (69%) (Table:9) which coincides with the study conducted by Jsitzia, L Huggins(1998) reported that the most common A.D.R. associated with cyclophosphamide is alopecia followed by fatigue. Burning micturition in 15 patients (46%). Fatigue in 17 patients (53%). Hematuria which less only in 5 patients (15%). Impaired vision in 1 patient (3%), which is a rare A.D.R. of doxorubicin.

General A.D.R. reported in all 4 cycles is fatigue in 17 patients (53%), light headiness is more in patients 30 patients (92%), and sore throat only in 13 patients (38%) (Table:11).

General A.D.R. reported in only 2 nd and 3 rd cycles showed in TABLE 12 severe alopecia was observed more in 33 patients (100%) followed by tissue extravasation in 16 patients (48%), burning micturition in 12 patients (36%), nail and skin discoloration in 13 patients (38%).

General A.D.R. reported in 2nd and 4thcycle showed more nail and skin discoloration in 10 patients (31%) impaired vision only in 1 patient (3%) (Table:13)which coincide with the study with Charles F Curran, James K Luce reported that conjunctivitis and impaired vision was associated with doxorubicin and tissue extravasation in 7 patients (21%) joint pains in 8 patients (24%).

The Gastrointestinal A.D.R. was shown in Table 14 nausea and vomiting occurred in all patients (100%), burning sensation, oral mucositis, loss of appetite occurred in 15 patients (46%), which is coincides with the finding of the study conducted by Greene, LM Nail (1994) reported that fatigue, nausea headache, mucositis, and diarrhea occurred in patients with A.C. and F.A.C. regimen. Diarrhea in 13 patients (38%). Constipation in 5 patients (15%). We concluded that most GI ADR is nausea and vomiting observed in all patients, followed by burning sensation and appetite loss.

Gastrointestinal A.D.R. was reported in all four cycles, which showed the occurrence of nausea and vomiting in 33 patients (100%), followed by loss of appetite and burning sensation in 15 patients (46%) (Table: 15).

Gastrointestinal A.D.R. reported in only 2nd and 3rdcycle is black stools in 11 patients(33%) followed by constipation and oral mucositis in 5 patients (15%) and diarrhea in 8 patients(24%) as shown in Table:16.

Gastrointestinal A.D.R., which was reported only in the 4th Cycle, was oral mucositis in 10 patients (30%), diarrhea in 5 patients (15%), and black stools in 4 patients(12%)due to excessive gastric ulcer as shown (Table:17).

Hematological changes will mainly occur in breast cancer patients receiving Adriamycin +cyclophosphamide regimen; hematological changes are anemia, leucopenia, and thrombocytopenia, which coincide with the study with Robert J Cersosimo.

Hematological changes after cycle-1 found mild anemia in 8 patients (23%), moderate in 3 patients (8%), and no severe anemia was found. No leucopenia and thrombocytopenia were found after cycle 1, as shown in Table: 18.

Hematological changes after cycle 2 show mild anemia in 8 patients (23%) and moderate anemia in 3 patients (8%). No severe anemia was found, and also no leucopenia and thrombocytopenia were found after cycle 2, as shown in Table: 19.

Hematological changes after cycle 3 showed in Table20 the mild anemia was demonstrated in 8 patients (23%) and moderate anemia in 3 patients (8%); no severe anemia leucopenia and thrombocytopenia were found after cycle 3.

Hematological changes after cycle 4 were mild anemia in 12 patients (38%), moderate anemia in 9 patients (24%), and no severe anemia was found. The mild leucopenia was found in 8 patients (23%) moderate, and severe leucopenia is absent. The mild thrombocytopenia in 9 patients (24%) no moderate and severe thrombocytopenia (Table: 21).

In gastrointestinal A.D.R. management for the burning sensation, which occurred in 15 patients (46%), management was done by giving Syp. Antacid (aluminum and magnesium) 5ml, whereas for nausea and vomiting in 33 patients (100%), management is done by giving Tab. Ondansetron 4mg. For diarrhea in 13 patients (38%), management was done by giving Tab. Metronidazole. 400 mg. Oral mucositis in 15 patients (46%) management was done by providing cryotherapy and mouth gargle. For loss of appetite, no management was done. For constipation, 5 patients (15%) management by cremaffin 5ml was done, whereas, for black stools, no management was done, as shown in Table: 22.

In general, A.D.R. management alopecia was found in all patients (100%) management is wearing a cap or wings. Burning micturition in 15 patients (46%) management by syp potassium citrate 1100mg+ magnesium citrate 375 mg+hydrochloride 20 mg was done. Fatigue in 17 patients (53%) management was done by giving diet modification and iv hydration (Table: 23).

Hematuria in 5 patients (15%) management is to drink more fluid daily. Sore throat in 13 patients (38%) management by saline gargle. No management is done for tissue extravasation, swelling of lips and face, impaired vision, and nail and skin discoloration (Table:23).

Joint pain in 15 patients (46%) management by analgesics (topical), Tab.paracetamol 650mg. lightheadedness and dizziness in 30 patients (92%) were managed by tab paracetamol 650 mg, as shown in Table: 23.

V. CONCLUSIONS

Our study was conducted for 6 months, and data of 33 patients who satisfied the inclusion criteria were analyzed in a prospective manner. Cardiac safety analyses of Adriamycin + Cyclophosphamide (A.C.) regimen in breast cancer patients were evaluated. Adverse drug reaction occurred with A.C. regimen were reported and monitored the management for Adverse effects.

Our study demonstrated that breast cancer incidence is greater in the age group of 51-60 years, followed by 41-50 years.

Patients were categorized into ductal and lobular, ductal, invasive ductal, and duct carcinoma based on morphology. They found that most patients had invasive ductal carcinoma, followed by ductal and duct carcinoma.

The majority of our study patients were diagnosed with Stage 3 (54%), followed by stage 2 (46%) breast cancer.

In our study, we analyzed for cardiac safety of the A.C. regimen. We found moderate Hypertension in 15 patients and mild Hypertension in 14 patients in the first Cycle of the A.C. regimen. In the 2nd Cycle of the A.C. regimen, 20 patients had mild Hypertension, and 4 had moderate Hypertension. In the 3rd Cycle, both Hypertension and hypotension were found in patients.

LVEF changes were monitored from ECHO and found that 7 had mild change followed by moderate and severe LVEF changes.

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