

## A survey on gastrointestinal adverse drug reactions of Doxorubicin and Cyclophosphamide combination therapy

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### Abstract

Adverse drug reactions (ADRs) are very common with anticancer drugs. The objectives of the survey are to evaluate ADRs of AC (Adriamycin (Doxorubicin) and Cyclophosphamide) combination therapy with special reference to GIT (Gastrointestinal system). It was a prospective, descriptive, observational study which included 90 female patients receiving AC combination therapy for their treatment through a purposive sampling and from 01-01-2016 to 31-12-2016 at Cancer Hospital Jamshoro Pakistan. Patients were interviewed during follow up session with a consultant, their response was recorded in a questionnaire and verified through British National formulary (BNF), Hartwig & Siegel scale (ADR severity assessment scale). The survey results shows that AC anticancer combination therapy can result in various disturbances in gastrointestinal tract among which nausea, vomiting decreased appetite and hyperacidity were most common. These must be taken into account and managed with supportive treatment in order to maintain better quality of life during the cancer treatment.

**Keywords:** GIT, ADRs, Drugs, Cancer, Anticancer drugs, AC therapy Doxorubicin, Cyclophosphamide.

### Introduction

Gastrointestinal system (GIT), a vital organ system helps to process food, nutrients and to maintain the healthy lifestyle of an individual. GIT disorders are common in developed and developing countries and their development can affect the quality of life.<sup>1</sup> These disorders of GIT can result from variety of the factors which include: unnecessary food intake which is unable to be digested by system, high stress which affect the secretions of GIT and can alter the environment of digestive system, improper exercise, in some individuals travelling and the drugs administered orally or by other route for systemic effect.<sup>1-3</sup>

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Cancer patients treated with chemotherapeutic agents have high susceptibility to develop GIT disorders when administered as a single agent as a result of effect upon normal cells.<sup>4-6</sup> The situation is prone to even more worse response when a multiple dosage regimen is used for improved efficacy especially when patient is suffering from Advance Disease level. Breast cancer one of the most frequent cancer type among females and treatment involves various combination therapies in which AC is one of most frequent therapy prescribed by physicians especially for the treatment of breast cancer.<sup>7</sup> AC stands for Adriamycin (doxorubicin) and Cyclophosphamide which is given in cycles which are repeated every 21 days and usually four cycles are given. Adriamycin/ Doxorubicin belongs to anthracycline anticancer antibiotic group, whereas Cyclophosphamide belongs to the class of alkylating agent. Both drugs have similar cytotoxic effect as both interfere with synthesis of DNA of the cells not only tumour cells but also normal cells especially those which divide rapidly and therefore affecting the organs with rapid cell division. One of the important systems affected is the gastrointestinal tract and therefore patients are at high risk to develop various gastrointestinal symptoms as a result of disturbance in their functioning of the cells by the Anticancer drugs. Common adverse effects of these anticancer agents reported in standard literature include: nausea, emesis, mouth sores, dyspepsia, diarrhoea etc. Various clinical trial studies reports showed that the different anticancer agents cause various effects among which the gastrointestinal tract problems are more frequent as compared to other effects in patients of developed countries.<sup>6,8-11</sup>

### Methods

A prospective observational survey was conducted on 90 breast cancer patients on AC (Adriamycin/Doxorubicin, Cyclophosphamide) therapy at the dose of 60/600mg/m<sup>2</sup> with prophylactic anti-emetic treatment as per ESMO guidelines for moderately emetogenic therapy at Cancer Hospital Jamshoro Pakistan through a purposive sampling method from 01-01-2016 to 31-12-2016. All the patients were interviewed during follow up session with consultant and the response was recorded in a questionnaire. The results were compared with British

National formulary (BNF)<sup>5</sup> 2012 and severity assessed via Modified Hartwig and Siegel Scale. The survey was conducted in accordance with the Principles of declaration of Helsinki.

The inclusion criteria consisted of female patients receiving AC combination therapy for breast cancer treatment (Adjuvant curative protocol) aged above 18 years.

**Exclusion Criteria:** Any patient receiving another protocol for treating any other severe condition such as HIV, Tuberculosis, Hepatitis, any precondition associated with malignant disease or other related factor which could affect the accuracy of results, neurological diseases, unable to respond were excluded from study to avoid ambiguity of response.

## Results

The survey results included 90 patients, 80% having an invasive type of cancer. The age group of majority of population were above 40 and up to 50 years as shown in Table-1 with the mean age of 43.522±9.922 Table-2 represents the occurrence of various adverse-effects related to GIT secondary to administration of AC protocol. Each patient responded differently towards the therapy and showed various combinations of these gastrointestinal disorders. All the ADRs reported by the patients were compared with standard reference BNF and severity assessed in modified Hartwig and Siegel scale and those severe enough as level 2 or greater were included in the survey. This helped to evaluate not only

**Table-1:** Age group distribution.

Age (in years)	Patients	Frequency (%)	Cumulative (%)
18-30	7	7.778	7.778
31-40	23	25.555	33.333
41-50	45	50	83.333
51-60	8	8.889	92.222
61 and above	7	7.778	100

**Table-2:** Frequency of gastrointestinal disturbances.

Sr. No	ADRs	No of Patients	Frequency (%)
1	Nausea	63	70
2	Vomiting	54	60
3	Indigestion	45	50
4	Hyper acidity	55	61.111
5	Decreased Appetite	59	64.444
6	Abdominal pain	25	27.778
7	Mouth sore	18	20
8	Diarrhoea	12	13.333

the ADRs associated but also the severity to develop a complete picture of local patients response towards the combination therapy (Table-2). Represents the percentage of gastrointestinal disorders from which patients suffered during the anticancer therapy.

The manner in which these ADRs reported by the patients are presented in Table-2. Nausea appeared to be the most common problem (70%) whereas vomiting was the 3rd most common problem, which either appeared as breakthrough symptoms and/or symptoms relapsed after few hours of chemotherapy and these persisted for more than 24hours in majority of the patients after every cycle. Decreased appetite appeared 2nd frequent problem and majority of the patients suffered for more than 24 hours even up to 72 hours. Hyperacidity, indigestion and pain in the abdominal also affected a large number of patients and persisted for 24-48 hours after each cycle. Mouth sores appeared in a small number of patients and majority of them showed a level of 2 ADR. Diarrhoea was also less frequently encountered. ADRs were included in the data if symptoms persisted for more than 24 hours. Majority of patients were of level 2 ADR in scale.<sup>12</sup>

## Discussions

Our study identified multiple ADRs associated with the digestive tract among the local population and by comparing them with the other studies was found to be 70% and 60% respectively. Similarly diarrhoea presented as an uncommon ADR in 6-20% patients and in our cases it was 13.333%. Mouth sores were reported by 20% of the patients and they were of a severe form requiring medical intervention. Present findings show that people from developed as well as developing countries can equally suffer from these ADRs of digestive tract with little difference.<sup>6</sup> As per NCCN, ASCO, ESMO's updated guidelines (2016-17), which classified AC as highly emetogenic regimen with response rate >90% but present study subject's response was moderate.<sup>13-17</sup>

Present study results shows that in our population AC therapy can be considered as a moderately emetogenic regimen (response rate <90%) along with other gastrointestinal ADRs. The health professionals can manage them with supportive therapy by following the guidelines that best suits the patient, to maintain a better quality of life during the cancer treatment as well as can reduce health and economic burdens associated with therapy.

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