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Hepatotoxicity Assement in Breast Cancer patients receiving Doxorubicin Chemotherapy

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Abstract:
Background: *Hepatic dysfunction in the cancer Dept has a significant impact on patient outcomes. The therapeutic application of Anthracycline antibiotics is limited by side-effects mainly chronic Cardiotoxicity, Myelosuppression, and Hepatotoxicity.*
Aim: *To Analyse the risk of Hepatotoxicity in Breast cancer patients receiving Inj. Doxorubicin.*
Subjects and Methods: *The investigation was a prospective study that was conducted in cancer patients receiving Inj. Doxorubicin doses of 50 mg/m^2, and 75 mg/m^2 at a South Indian tertiary care hospital. Sample collection was done from pre-chemotherapy to 4th cycle. SGPT, SGOT,*
Direct Bilirubin and Total Bilirubin were assessed to determine Hepatotoxicity. Data were analyzed using unpaired t test, Pearson correlation using GraphPad Prism version 5.00.
Results: *Breast cancer patients comprised 37% (49/132) of the total female cancer patient population, of which 46 patients with mean age of 46.61 (13.39) years were included and 30.4% (14/46) patients were developed hepatotoxicity. The mean (SD) of SGOT, SGPT, Direct Bilirubin, Total Bilirubin in pre-chemotherapy cycle to fourth chemotherapy cycle were found to be 21.97 (5.798) U/L and 181.3 (103.6) U/L, 23.17 (6.237) U/L and 147.6 (90.9) U/L, 0.1351 (0.1186) mg/dL and 0.5445 (0.4587) mg/dL, 0.3094 (1.346) mg/dL and 2.7163 (1.898) mg/dL simultaneously where P < 0.05 which were statistically significant.*
Conclusion: *There exist a strong correlation between the use of Inj. Doxorubicin and risk fordeveloping hepatotoxicity. The healthcare professionals dealing with breast cancer patients need to have awareness for hepatotoxicity with the use of Inj. Doxorubicin therapy.*
Keywords: *Breast cancer, Doxorubicin, Hepatotoxicity, South India, Patient outcomes*

I. Introduction

Occurrence of organ dysfunction is a common phenomenon in the cancer unit and hepatic dysfunction in the cancer unit has a significant impact on patient outcomes and represents a substantial healthcare burden which requires consideration of hepatic function and probable or proven site of chemotherapy.[1] The therapeutic application of anthracycline antibiotics is limited by its side-effects mainly dose-dependent chronic cardiotoxicity and myelosuppression.[2]

Doxorubicin (Adriamycin) is commonly used in the treatment of a wide range of cancers including some Leukaemias and Hodgkin's lymphoma as well as cancers of the Breast, stomach, lung, ovaries, soft tissue sarcoma, multiple myeloma and others.[3] The exact mechanism of doxorubicin is complex and still somewhat unclear, though it is thought to interact with DNA by intercalation and inhibition of macromolecular biosynthesis.[4,5]

Hepatotoxicity can reproduce necrosis, steatosis, fibrosis, cholestasis, and vascular injury.[6]

Liver injury caused during cancer chemotherapy treatment doesn't always reflect hepatotoxic anticancer drugs, but also antibiotics, analgesics, antiemetics or other medications. Host's susceptibility to liver injury may be affected by pre-existing medical problems, tumor, immunosuppression, hepatitis viruses and other infections, and nutritional deficiencies or total parenteral nutrition. So, it is difficult to attribute liver injury to a toxic reaction.[7,8] Even though the liver performs many metabolic functions, yet proper quantitative markers for liver function are not available in the routine practice. The stage or characterization of acute hepatotoxicity is mainly based on liver biopsy.[9] There are many pharmaceuticals which can cause liver injury, but most hepatotoxic drug reactions are idiosyncratic either by immunologic mechanisms or variations in host metabolic response.[10] All these reactions are not typically dose-dependent. In general, pre-existing liver disease has little effect on elimination and toxicity of most drugs.[11,12]

Doxorubicin containing drug regimens are widely used in patients in breast cancer.[13] The incidence of the most common diverse toxicities resulting from its chemotherapy can be described as cardiotoxicity, hepatic, haematological and testicular toxicity.[14] The following study specifically evaluated the incidence of hepatotoxicity with the use of Inj. Doxorubicin.

II. Subjects and Methods

The investigation was a prospective, analytical study that was conducted at Mahatma Gandhi Memorial (MGM) Hospital with prior approval by the Human Ethics Committee for Human Experimentation of MGM Hospital/Kakatiya Medical College, Warangal, Andhra Pradesh, India. This study was conducted among 49 consecutive treatment group receiving 4 cycles of chemotherapy with Inj. Doxorubicin from January 2011 to May 2011. Sample size was calculated depending on the assumption to assess the hepatotoxicity, based on standard deviation calculation (Probability=95%, P = 0.05). Patient recruitment is based on review of case sheets, findings from clinical assessment and final judgement of chief oncologist with recommended Inj. Doxorubicin doses of 50 mg/m^2, and 75 mg/m^2. Hepatotoxicity can be attributed to Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) greater than three times the normal range or an increase of Bilirubin greater than 1.5 mg/dL. Inclusion criteria were age greater than 19 years and have received Inj. Doxorubicin at one of the conventional doses. Exclusion criteria were the ambulatory patients, terminally ill patients and development of hepatic dysfunction prior to Inj. Doxorubicin administration.

During data collection patients were informed about the study using patient information format and the written consents were obtained from the patient or their caregivers through patient consent form which was previously designed. Baseline demographics were collected including age, baseline haemoglobin and serum creatinine. Blood sample collection was done at prechemotherapy and follow-up was done up to 4^{th} cycle.

III. Statistical Analysis

All the data were analyzed using unpaired t test, Pearson correlation using the software GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com. P values $P < 0.05$ were considered statistically significant.

IV. Results

Breast cancer patients comprised 37% (49/132) of the total female cancer patient population, of which 46 patients with mean age 46.61 (13.39) years were included based upon the predefined inclusion/exclusion criteria. Habitat of the patients revealed that 76.08% were having rural background and 23.91% (11/48) were from urban areas.

The main reasons for admission include nipple discharge in breast among 84.78% (39/46) and lumps in the breast among 15.21% (7/46) patients. Body mass index of study population has shown that 36.95% (17/46) of the patients were having underweight. Of the patients included into the study, 30.4% (14/46) developed hepatotoxicity based upon the predefined criteria. There were no additive correlates for this adverse effect.

SGPT: The mean (SD) of SGPT in pre-chemotherapy cycle to fourth chemotherapy cycle was observed to be 23.17 (6.237) U/L and 147.6 (90.9) U/L where the $P < 0.001$ which is statistically significant .SGOT: The mean (SD) of SGOT in pre-chemotherapy cycle to fourth chemotherapy cycle was observed to be 21.97 (5.798) U/L and 181.3 (103.6) U/L where the $P < 0.001$ which is statistically significant .Total Bilirubin: The mean (SD) of total bilirubin in pre-chemotherapy cycle to fourthchemotherapy cycle was observed to be 0.3094 (1.346) mg/dL and 2.7163 (1.898) mg/dL where $P = 0.032$, which is statistically significant .

Direct Bilirubin: The mean (SD) of Bilirubin in pre-chemotherapy cycle to fourth chemotherapy cycle was observed to be 0.1351 (0.1186) mg/dL and 0.5445 (0.4587) mg/dL where the $P = 0.041$ which is statistically significant.

Similarly the mean (SD) values for liver function tests of hepatotoxic and non-hepatotoxic patients were compared and found that there exists a highly significant ($P < 0.001$) difference between those two groups..

V. DISCUSSION

Liver dysfunction or liver damage, which is associated with an overload of hepatotoxins or hepatotoxicants is known as Hepatotoxicity.[15] Breast cancer is having a major proportion among all type of cancers in this study site and majority of them are from low-socioeconomic status with little knowledge about the risk factors of cancer.[16] Age distribution of the study population at this study site has shown that adult population was mostly affected. A majority of the patients were having rural background, which constitutes about 76.08% (35/46) since this study site is having more rural areas surrounding it and 23.91% (11/46) patients came from urban areas. Among the total patients only 2.71% (1/46) were unmarried, 76.08% (35/46) were married and living with partner and 21.73% (10/46) were divorced/separated/widowed. As the social status is having a direct relationship with the risk of getting cancers, we collected the information regarding social status of the patients with personal interview. In our study group 13.04% (6/46) were having habit of alcoholism, 15.21% (7/46) were having habit of smoking, 23.91% (11/46) were having both alcoholism and smoking, 6.52% (3/46) were having the habit of chewing Pan/Gutka/Tobacco and 41.30 % (19/46) were having clean habits. These findings are similar to the past studies in South India.[17]

Of the total population, most of the patients were illiterate which accounts for 69.56% (32/46),

21.73% (10/46) were having primary educational status, 8.69% (4/46) were having secondary level educational status. Higher educational status was zero in this patient group. These results are showing the poor educational status of this study group. Menopausal status has shown that the 43.47% (20/46) were in pre-menopausal status, 50% (23/46) were having post-menopausal status and the menopausal status of 6.52% (3/46) patients is unknown because of reasons like unwillingness of patients to reveal. Occupationally 36.95% (17/46) patients were housewives,

21.73% (10/46) were agricultural labors, 6.52% (3/46) were farmers 34.78% and (16/46) were daily wages. As revealed by the patients the reasons for admission include nipple discharge in breast among 84.78% (39/46) patients, lumps in the breast among 15.21% (7/46) patients. These are the main symptoms they had experienced before the exact diagnosis of breast cancer. Body mass index of the patients were calculated during patient recruitment and found that 36.95%
(17/46) were underweight, 56.52% (26/46) were having normal weight and 6.52% (3/46) were having overweight. There were no obese patients in this study group. Since the prevalence of
underweight was more among these patients, there is a great need to provide dietary counselling based on their financial and educational status.[18]

Elevation of liver enzymes and function tests can often be difficult to determine in a patient clinical setting. Our investigation revealed that the incidence of hepatotoxicity associated with Inj. Doxorubicin was 30.4% (14/46) based upon our predefined criteria which were supported by the study of Llesuy SF and Arnaiz SL.[19] In a study by Yang XL et al almost 40% of the patients suffered liver injury after doxorubicin treatment.[20] Inorder to evaluate hepatotoxicity in the study group, liver function tests such as, SGOT, SGPT, Direct Bilirubin, Total Bilirubin were assessed from pre-chemotherapy to completion of four chemotherapy cycles. Our criteria of utilizing elevation of transaminases and bilirubin have been reported by other investigators prior as a surrogate for liver function during drug therapy.[21] In this study the mean (SD) of the SGOT in pre-chemotherapy cycle and fourth chemotherapy cycle were found to be 21.97 (5.798) U/L and 181.3 (103.6) U/L simultaneously which is a significant increase ($P < 0.001$). Mean (SD) of SGPT was found to increased significantly ($P < 0.001$) from 23.17 (6.237) U/L to 147.6 (90.9) U/L. Direct Bilirubin was increased from 0.1351 (0.1186) mg/dL to 0.5445 (0.4587) mg/dL and Total Bilirubin was increased from 0.3094 (1.346) mg/dL to 2.7163 (1.898) mg/dL where $P < 0.041$ and $P < 0.032$ simultaneously which were statistically significant. After controlling for concurrent hepatotoxic exposures (chemotherapy) there were no correlates (eg. hemoglobin) for this adverse drug event when utilizing a multivariate logistic regression model.

Prior investigations by Llesuy SF and Arnaiz SL have determined that the administration of doxorubicin produced increases of 51% and 53% in liver spontaneous chemiluminescence and malonaldehyde formation respectively.[19] Characteristics of the population were an elevation in serum transaminases and bilirubin. The proposed mechanism for this observation centers on the free radical hypothesis that Doxorubicin undergoes one-electron reduction through NADPH cytochrome P-450 reductase and decreases in antioxidant enzyme, Superoxide dismutase and catalase activity while increase in the malondialdehyde levels.[19,22,23] Similarly the mean (SD) values of SGOT, SGPT, Direct Bilirubin, Total Bilirubin of patients who have developed hepatotoxicity and patient group who didn't developed hepatotoxicity were compared and found that there exists a highly significant ($P < 0.001$) difference between those two groups with reference to all liver function tests. Based on this study, it appears that Inj. Doxorubicin have thepotential to develop hepatotoxicity, and precautions should be taken including optimizing the dosage pattern, providing appropriate concentration, dosage and treatment schedule of antioxidants like Vitamin E, Vitamin C, Vitamin A, antioxidant components of Virgin Olive Oil and Selenium as dietary supplements as well as administration as chemotherapeutic agents, by which the anti-tumor action can be maximized and toxicity especially hepatotoxicity of Inj. Doxorubicin can be minimised.[24,25]

Limitations of the study

The first limitation was that the cohort used to define our patient population for this study was split between the intensive care unit and oncology medicine floor at 24% and 76% respectively.
Additional limitations include that the study is single-centered and contains relatively small number of patients. Another limitation of the study was that to truly see the effect of Inj.

Doxorubicin on liver, it should be the only exposure to the patient. However, patients that would require Inj. Doxorubicin therapy may be exposed to additional hepatotoxins. The patient population that are receiving chemotherapy often have underlying disease process (i.e., cancer)and/or exposure to risk factors (i.e., medications, intravenous contrast) for the development of hepatotoxicity.

VI. Conclusion

From these results we can conclude that there exist a strong correlation between the use of Inj. Doxorubicin and risk for developing hepatotoxicity among the breast cancer patients at this study site. These findings are showing that the healthcare professionals need to have awareness for hepatotoxicity with the use of

Inj. Doxorubicin therapy. A weakness of our analysis is that it may not include the staistical correlations of sociodemographic factors like age, dose escalation, or cumulative dose. There are a multiple reasons for and consequences of hepatotoxicity in this population and there is a need for future interventions to target each specific aspect of hepatotoxicity.

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