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Original Article

Utility of Monitoring Renin And Aldosterone Levels In Determining Efficacy of Chemotherapy

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ABSTRACT

Objective: To determine the clinical utility of renin and aldosterone levels in cancer patients treated with combination of ACE inhibitors and anthracyclines

Study Design: Quasi-experimental study

Place and Duration of Study: Department of Chemical Pathology, Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan, from Jul to Dec 2020.

Methodology: Patients of either gender, aged between 40-70 years, who were diagnosed with various malignancies and were on anthracyclines as part of chemotherapy for last six months were enrolled and further divided into two groups. Group I patients were given anthracyclines alone, Group II patients were given ACE (Angiotensin-Converting Enzyme) inhibitors along with anthracyclines. Samples were collected and analyzed for Active Renin Concentration (ARC), plasma aldosterone, troponin I and N-terminal pro-B-type natriuretic (NT-proBNP) peptide. Mean values of these parameters amongst two groups were compared by applying independent sample t test where p-value ≤ 0.05 was considered as significant.

Results: Out of 195 patients 114(58.5%) were in Group I and 81(41.5%) were in Group II. Mean values of plasma aldosterone (799.84 ± 56.88 pmol/L vs 430.59±62.36 pmol/L), ARR (Aldosterone-to-Renin Ratio) (46.24±21.80 pmol/mIU vs 25.77±7.10 pmol/mIU), Pro BNP (125.26±10.61 pg/ml vs 87.77 ± 8.76 pg/ml) and trop I (0.06±0.011 ng/ml vs 0.04±0.007 ng/ml) were higher in Group I as compared to Group II. The difference among means of each parameter amongst two groups was found to be statically significant (*p*-value≤ 0.05).

Conclusion: Plasma aldosterone, ARR, Trop I and NT pro BNP levels can be used for monitoring and early detection of Anthracycline-Induced Cardiomyopathy (AIC).

Keywords: Aldosterone, Angiotensin-Converting Enzyme Inhibitors, Anthracyclines, Brain Natriuretic Peptide, Renin

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INTRODUCTION

Cancer is one of the main causes of death worldwide with the number of cancer patients having increased over time in both developed and developing countries due to smoking, physical inactivity, improper diet, decreased number of pregnancies, aging population and advancement in socioeconomic development.[1] The World Cancer Report published in 2014 by World Health Organization (WHO) revealed that the number of new cases of cancer was about 14 million globally in 2012, which is expected to increase to 19.3 million by 2025 with Lung cancer (13%) being the most common, followed by breast (11.9%), colorectal (9.7%) and prostate (7.9%) cancer.[2] Cancer is an emerging threat and poses a significant health burden in Pakistan where the total number of cases reported in Pakistan in 2012 were 0.14 million out of which 57.2% were female while 42.8% were male, making the cancer the leading cause of death caused by non-communicable disease.[3] One of the major components of cancer treatment is chemotherapy with anthracyclines, which are used for various malignancies such as leukemia, lymphoma, breast cancer, and soft tissue sarcoma, but their utility is often compromised due to cardiotoxic effects, leading to cardiomyopathies, pericarditis, left ventricular dysfunction and subsequently heart failure.[4] Dysregulation of Renin-Angiotensin-Aldosterone System (RAAS) is paramount in development of cardiotoxic effects of anthracyclines,[5] thus, RAAS inhibiters, such as Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) are widely used along with anthracyclines. Several trials have utilized ACE inhibitors, ARBs, or β-blockers during and after chemotherapy.[6] In Pakistan few studies have been carried out to determine the role of RAAS inhibition in relation with chemotherapeutic drugs. Our study was, therefore, conducted to determine the clinical utility of renin and aldosterone levels as a marker for monitoring and

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early detection of anthracycline induced cardiac toxicity in patients treated with anthracyclines.

METHODOLOGY

The Quasi-experimental study was conducted at Department of Chemical Pathology, Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan, over a period of six months from July to December, 2020 after gaining approval from the Institutional Ethics Committee (FC-CHP19-17/READ-IRB/21/142). Sample size was calculated by using World Health Organisation (WHO) sample size calculator with 95% confidence interval and 5% margin of error taking 14.9% as prevalence of leukemia in Pakistan.[7] A total of 195 patients were enrolled in our study using non-probability sampling technique.

Inclusion Criteria: Patients of either gender, aged between 40-70 years, were diagnosed with any type of malignancy such as leukemia, Hodgkin lymphoma, breast or bladder cancer and were on anthracyclines as part of chemotherapy for last six months.

Exclusion Criteria: Patients with comorbidities such as diabetes, adrenal and renal disorders were excluded.

On the basis of treatment modalities, patients were divided into two groups, where Group I included patients who were being treated with chemotherapy (anthracyclines) alone while Group II included patients who were given ACE inhibitors, such as Captopril and Enalapril, as prophylactic treatment for cardiotoxicity along with chemotherapy (anthracyclines). After taking written informed consent, 3 ml of blood sample was collected in K3 EDTA tube for estimation of Active Renin Concentration (ARC), plasma aldosterone, Troponin I and N-terminal pro-B-type natriuretic (NT-proBNP) peptide. Aldosterone Renin Ratio (ARR) was calculated by dividing plasma aldosterone level over ARC. Sample centrifugation was done at 3500 rpm for 3 minutes as plasma was separated and analyzed within thirty minutes of collection. The analysis was done on ADVIA Centaur XP using chemiluminescence as analytical technique where two levels of controls, low and high, were run on instrument and were plotted daily. Statistical analyses were performed using IBM Statistical Package for the social sciences (SPSS) version 26.0. On applying Shapiro-Wilk test, the data was found to be normally distributed (p-value > 0.05). Frequency and percentage were used for qualitative variables such as gender and number of cases in each group while quantitative variables such as age, aldosterone level, ARR, trop I, systolic and diastolic blood pressure were expressed as Mean±SD. Mean values of these variables among two patient groups were compared by applying independent sample test where p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

A total of 195 samples were included in the study out of which 111(56.9%) were male while 84(43.1%) were females. Mean age of patients was 57.15±8.97 years. Out of 195 patients, 114(58.5%) were treated with chemotherapy alone (Group I) and 81(41.5%) were treated with ACE inhibitors along with chemotherapy (Group II). Distribution of various malignancies among all patients is illustrated by Fig-1. Mean values of plasma aldosterone, ARR, trop I and Pro BNP were higher in patients of Group I as compared to patients of Group II. The difference of means between each variable amongst the two groups was found to be statically significant with p-value ≤ 0.05, as shown in Table-I.

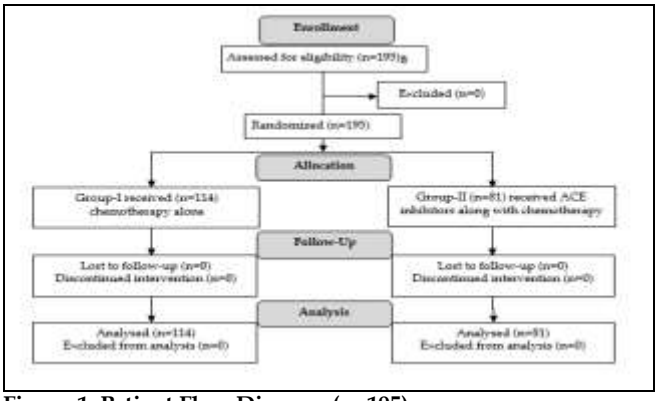

Figure-1: Patient Flow Diagram (n=195)

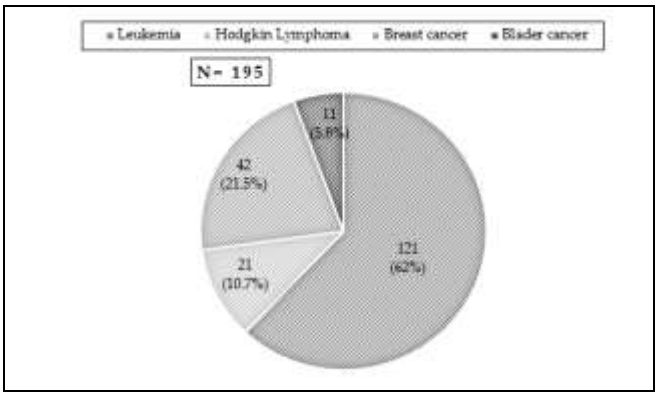

Figure-II: Distribution of various malignancies (n=195)

DISCUSSION

With approximately 10 million deaths in 2020 alone, cancer is a leading cause of mortality

worldwide.[8] Chemotherapy is a therapeutic modality of cancer management involving the administration of chemical agents to kill malignant cells, but the effective use of chemotherapy requires an in-depth consideration of the principles of tumor biology, pharmacology, cellular kinetics, and drugs resistance.[9] Among the most effective chemotherapeutic agents available at present are anthracyclines, derived from a gram positive bacterial species of the genus Streptomyces.[10] Anthracyclines available for treatment include Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone, and Valrubicin, with their chemotherapeutic regimens as various combinations playing a pivotal role as cancer treatments, including breast cancer patients (32% of cases),[11] lymphoma (57-70% of elderly patients,[12,13] 50-60% of pediatric cancer survivors),14 bladder cancer and other metastatic cancers.[15] In addition to solid tumors, anthracyclines are also employed in hematological malignancy management protocols for both Acute Lymphoblastic and Myeloid Leukemias.[16] The cytotoxic effects of Anthracyclines are exerted via a variety of mechanisms. Most significant are the effects of interaction between anthracyclines and DNA Topoisomerase isomers II-α and II-β, leading to inhibition of DNA replication and apoptosis.[17] However, anthracyclines are notorious for their cardiotoxicity.[18] Doxorubicin increases the activity of Angiotensin-II (AgII) by increased synthesis or enhanced receptor signaling which is related to Anthracycline Induced Cardiotoxicity (AIC) in murine models.[19] In our study, we found that the levels of aldosterone, ARR, Trop-I and NT Pro-BNP were higher in patients who were administered anthracyclines without ACE inhibitors (Group I) as compared to patients who received ACE inhibitors along with anthracycline (Group II). The patients in Group I had their ARR and aldosterone levels raised and were prone to hypertension and cardiotoxic effects which was further investigated by analyzing Trop I and NT pro BNP of same patients and found raised. In patients of Group II, the ARR and aldosterone levels were within normal range as were the cardiac biomarkers. In one randomized control trial, it was found that after six months of chemotherapy, Left ventricular ejection fraction (LVEF) decreased more in placebo (Group B) as compared to patients who received combination of Enalapril along with anthracyclines (Group A) since start of treatment, however, there was no significant difference in CK MB levels.[20] Another study noted 21 that the decline in LVEF was more in patients who were given anthracyclines alone (5.52 ± 8,90 %) as compared to those who were given lisinopril and bisoprolol along with anthracyclines (0.27 ± 5.73 %) as a prophylactical regimen against AIC. Our study was in concordance with other studies which were conducted to evaluate the monitoring of Aldosterone, ARC, ARR, Trop I and NT pro BNP for early detection of cardiotoxic effects of anthracyclines hence leading to better treatment outcome.

Table-I: Comparison of Means amongst Both Groups (n=195)

	Group I (n=114) (Mean ± SD)	Group II (n=81) (Mean ± SD)	*p*-value (≤ 0.05)
Aldosterone (pmol/L)	799.84 ± 56.88	430.59 ± 62.36	<0.001
ARR (pmol/mIU)	46.24 ± 21.80	25.77 ± 7.10	<0.001
Pro BNP (pg/ml)	125.26 ± 10.61	87.77 ± 8.76	<0.001
Trop I (ng/ml)	0.06 ± 0.01	0.04 ± 0.01	<0.001
Systolic BP (mmHg)	132.07 ± 6.66	119.07 ± 5.77	<0.001
Diastolic BP (mmHg)	90.05 ± 5.90	80.62 ± 5.02	<0.001

**SD: Standard Deviation, ARR: Aldosterone-to-Renin Ratio, NT-proBNP: N-terminal pro-B-type natriuretic, Trop I: Troponin I*

LIMITATION OF STUDY

It was conducted in a single diagnostic center having a small group of patients. Therefore, a multicentric study with a large sample size may give a good representation of the desired comparison.

CONCLUSION

The concomitant use of ACE inhibitors with anthracycline-based chemotherapy demonstrates a significant protective effect, as evidenced by markedly lower levels of key cardiotoxicity biomarkers. Therefore, monitoring renin and aldosterone levels, alongside established biomarkers, provides clinical utility in objectively determining the efficacy of this chemotherapeutic regimen in mitigating cardiotoxicity.

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Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SAH & ZHH: Data acquisition, data analysis, critical review, approval of the final version to be published.

AIP & AB: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MWN & UA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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