Hepatotoxicity in Cancer Patients Receiving Anthracyclin at KAUH: A Retrospective Study

Naeem Qusty[1*], Adeel Chaudhary[2], Abduljawad Abdulshakor Khan[2], ShadiAlkhayyat[3], Mohamad Alhashmi[2], Rahaf Alshaikhi[4]

[1]Medical LaboratoriesDepartment, Faculty of AppliedMedicalSciences, Umm Al-QuraUniversity, Mecca, Saudi Arabia.
[2]Department of Medical Laboratory Technology, Faculty of AppliedMedical Sciences, KingAbdulazizUniversity, Jeddah, Saudi Arabia.
[3]Department ofMedicine, Faculty of Medicine, KingAbdulazizUniversity, Jeddah, Saudi Arabia.
[4]Biochemistry Department, Faculty of Science, King AbdulazizUniversity, Jeddah, Saudi Arabia.

ABSTRACT

Introduction: Drug-induced liver injury due to chemotherapy is an important cause of morbidity in cancer patients, although its clinical manifestations are poorly understood. It is known that liver metabolism has some phenotypical differences.Aim: To assess if we have any different profile of liver toxicity in cancer patients upon receiving first dose receiving Anthracyclines at King Abdulaziz University Hospital (KAUH). Patients and Method: This study was performed on 50 cancer patients who received anthracyclines at the department of Day Care Unit (DCU), KAUH, Jeddah between 2012 to 2017. The participants were selected based on predetermined inclusion criteria. The inclusion criteria were receiving anthracyclines chemotherapy (first dose) and the availability of patients' data before and after administration of anthracyclines. The sample collection procedures followed were in accordance with the local ethical guidelines. Patients date that obtained were; (age, gender, disease, therapeutic agent, administration date, results of liver function tests aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (T.Bil) before and after administration of anthracyclines). Results: Our results conveyed that the ALT, GGT, and T.Bil were the only parameters that provided statistical significance difference. AST results provided a borderline significance difference. ALP, TP and ALB results showed no significant difference. Conclusion: we failed to reject the null hypothesis and conclude that the liver function tests (ALT, AST, ALP, and T.Bil) are not increased after receiving the first dose of anthracyclines in cancer patients.

Key Words: Hepatotoxicity, Anthracyclin, Cancer Patients, KAUH.

eIJPPR 2020; 10(2):82-87

HOW TO CITE THIS ARTICLE: Naeem Qusty, Adeel Chaudhary, Abduljawad Abdulshakor Khan, ShadiAlkhayyat, Mohamad Alhashmi, Rahaf Alshaikhi(2020). "Hepatotoxicity in Cancer Patients Receiving Anthracyclin at KAUH: A Retrospective Study", International Journal of Pharmaceutical and Phytopharmacological Research, 10(2), pp.82-87.

INTRODUCTION

Cancer is a term that defines a group of diseases in which abnormal cells proliferate in an uncontrolled manner and invade nearby tissues. It can spread throughout the body by the lymph and blood systems [1, 2]. There are several types of cancer according to the type of cells that originate from [3]. Moreover, it is a globally devastating disease. [4] In 2012, the number of estimated cancer cases was 14.1 million worldwide. This horrifying number is expected to rise to 24 million by 2035 [5, 6]. Locally, in Saudi Arabia, according to the Saudi Cancer Registry, the number of cancer cases was 15,653 in 2013 [7].

Drug-induced liver injury due to chemotherapy is an important cause of morbidity in cancer patients, although its clinical manifestations are poorly understood. One of the options to treat cancer is the use of medications (chemotherapy) deliberately intended to be cytotoxic and consequently, causes negative side effects. Since the liver is the primary site of metabolism for many of these medications (chemotherapy), it is expected to have its share of negative side effects [7]. Monitoring liver function is helpful for patients starting new chemotherapy management. It is still a place of argument that how liver function testing should be performed and what implies

Corresponding author: Naeem Qusty
Address: Medical Laboratories Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Mecca, Saudi Arabia.
E-mail:✉nfqusty @ ugu.edu.sa
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 104 December 2019; **Revised:** 31 March 2020; **Accepted:** 07 April 2020

liver dysfunction. In the "Common Toxicity Criteria for Adverse Events," The National Cancer Institute (NCI) has classified toxicity grades into five grades according to the elevation of serum enzymes' activities. These serum enzymes are alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). Grade 1 (mild) if enzymes levels are > ULN (upper limits of normal) up to 2.5x ULN. Grade 2 (moderate) if these levels are > 2.5x to 5x ULN. Grade 3 (severe) if their levels are > 5x to 20x ULN; and grade 4 (life-threatening) if enzymes levels are > 20x ULN. Grade 5 (fatal) with no definition. Similarly, serum bilirubin concentration has been graded as (mild) if > ULN to 1.5x ULN, (moderate) if > 1.5 to 3x ULN, (sever) if > 3 to 8x ULN, and (life-threatening) if > 8x ULN. This practice of grading system is commonly used, but it still questionable if the elevation of these enzymes reflects the impairment function of the liver and therefore it can be misleading [7]. The Drug-Induced Liver Injury Network (DILIN), which started in 2004 [8], classified liver injury according to clinical measurements instead of laboratory values. Grade 1 (mild) in patients with an elevation of ALT and or ALP. Grade 2 (moderate) in case of elevated bilirubin and coagulopathy. Grade 3 (serious) if these patients hospitalized or unable to do their usual works. Grade 4 (acute liver failure) if another organ that is dependent on liver function displays dysfunction like the brain (encephalopathy), or kidney (renal insufficiency), and grade 5 (death or liver transplantation) [7]. There is a common agreement about the necessity for dose reduction for agents who rely on the liver metabolism for clearance from the bloodstream. Some chemotherapies must be used with extreme monitoring of liver function. These chemotherapies include anthracyclines, vinca alkaloids, taxanes, temsirolimus, imatinib, axitinib, lapatinib, erlotinib, nilotinib, pazopanib, ponatinib, and ruxolitinib [7]. Hepatotoxicity clinical presentations range from asymptomatic, an increase of liver function tests, cholestatic hepatitis, fibrosis and cirrhosis, malignant transformation, veno-occlusive disease, and hepatic failure,

Hepatotoxicity is a known side effect of chemotherapy [7], and it accounts for 10% of cases of acute hepatitis in adults' cancer patients [9]. One of the most common chemotherapies is Anthracyclines, and it ranks among the most effective chemotherapies in cancer treatment [10]. This retrospective study aims to assess if we have any different profile of liver toxicity in cancer patients upon receiving the first dose of Anthracyclines at King Abdulaziz University Hospital (KAUH). To accomplish this aim, a research hypothesis will be tested against its null hypotheses. The research hypothesis: the liver function tests (ALT, AST, ALP, and T.Bil) are increased after receiving the first dose of anthracyclines in cancer patients. On the contrary, the null hypothesis states that the liver function tests (ALT, AST, ALP, and T.Bil) are not increased after receiving the first dose of anthracyclines in cancer patients. This study is an effort to provide evidence (data) about the hepatotoxicity of Anthracyclines in a small Saudi sample. Such a study is important to accumulate a pool of data that could be used by physicians for better Anthracyclines' understanding and better management for cancer patients.

MATERIALS AND METHODS:

Samples:

This retrospective study was performed on 50 patients who received anthracyclines, mainly doxorubicin and epirubicin. These patients were diagnosed as cancer patients with a solid tumor and received chemotherapy at the department of the day-care unit (D.C.U), King Abdulaziz University Hospital (K.A.U.H), Jeddahbetween 2012 to 2017. The participants were selected based on predetermined inclusion criteria. The inclusion criteria were receiving anthracyclines chemotherapy (first dose) and the availability of patients' data before and after administration of anthracyclines. The sample collection procedures followed were in accordance with the local ethical guidelines. Patients' data obtained were; (age, gender, disease, therapeutic agent, administration date, results of liver function tests before and after administration of anthracyclines).

Biostatistics:

Statistical analyses were partially performed using Microsoft Excel. The normality test was performed using the Shapiro Wilk test (Shapiro Wilk Test-Web version) to evaluate whether patients' data followed a normally distributed population or not. Total protein (TP) data was the only set of data that followed the normal distribution curve. Therefore, only for TP, paired t-test (Microsoft Excel) was used to assess if there is a significant difference between the means of data sets (Pre. and Post) after the administration of anthracyclines. For the rest of the data, the Wilcoxon signed-rank test was performed (Social Science Statistics website). In all tests, the values $p<0.05$ were considered as statistically significant.

RESULTS

This retrospective study aims to assess if we have any different profile of liver toxicity in cancer patients upon receiving the first dose of Anthracyclines at KAUH. Clinical data (age, gender, disease, therapeutic agent, administration date)and lab results (ALT, AST, ALP, and T.Bil)of 50 cancer patients who received anthracyclines

(first dose) at the department of D.C.U, K.A.U.H, Jeddah between 2012 to 2017 were collected. Moreover, after applying the normality test, the pre-selected test data (ALT, AST, ALP, and T.Bil) were not following the normal distribution curve. Therefore, the data were analyzed using the Wilcoxon signed-rank test, and the p-values were reported. In all tests, the values $p<0.05$ were considered as statistically significant. The samples' clinical-pathological data were presented in Table 1.

According to the AST, ALP, ALT and T.Bil test results, and after applying the Wilcoxon signed-rank test, there was no statistically significant increase between the pre-anthracyclines and post-anthracyclines of AST and ALP results, while ALT results demonstrated a clear statistical significance increase and regarding the results of T. Bil presented a statistical significance decrease, Table 2. Due to the availability of data for *gamma-glutamyl transferase* (*GGT*), total protein (TP) and *albumin* blood (ALB), their results were examined statistically to find any significant difference that could be used to demonstrate the effect of the Anthracyclines (first dose) on these analytes. Based on the GGT results illustrated an obvious statistical significant increase between the pre-anthracyclines and post-anthracyclines data. Consequently, TP and ALB results presented no statistical significance difference between the pre-anthracyclines and post-anthracyclines data, Table 2.

Table 1. The clinical-pathological features (50 samples) of the study.

Characteristics	Number of patients	Percentages %
Age(Years)		
<41.5 (mean)	14	28
≥41.5 (mean)	6	72
Types of cancer		
Breast cancer	38	76
Other types of cancer	12	24
Gender		
Female	47	94
Male	3	6

Table 2: Statistical results of the research.

Test	No. of samples	Change	p-value	NCI grade
ALT	49	*Elevated* 30.6→ 37(IU/L)	0.00097(S)	Normal
AST	50	*Elevated* 25.1→9.7(IU/L)	0.07927(NS)	Normal
T.BIL	49	*Reduced* 6.2→ 5.3µmol/L	0.01191(S)	Normal
ALP	45	*No change* 89.4→ 89.1(IU/L)	0.40517(NS)	Normal
GGT	43	*Elevated* 33.3→ 41.7 IU/L	0.01222(S)	Normal
TP	45	*No change* 74.8→ 73.9g/L	0.13252(NS)	Normal
ALB	45	*No change* 34.7→ 34.1g/L	0.13136(NS)	Normal

T.BIL,Total bilirubin, NS, Not significant, S,significant

DISCUSSION

Drug-induced hepatotoxicity is a major dose-limiting adverse effect hindering the clinical application of many drugs. The U.S. Food and Drug Administration (FDA) had delayed many drug approval and withdrawn approved drugs from the market because of severe hepatotoxicities, such as bithionol cobalt salts, sulfathiazole and oxyphenisatin [10-12]. The mechanisms causing the increased hepatotoxicity of Anthracyclinare not well defined. Unfortunately, one of the options to treat cancer patients is chemotherapy, and one of the most effective, liver threatening and common chemotherapy is Anthracyclines [7, 10]. Anthracyclines have known hepatotoxicity side effects [7, 10]. Hepatotoxicity defined as a liver injury caused by the usage of chemicals. This liver injury comes from the detoxification function of the liver. This function is handled by hepatocytes (liver cells) that metabolize toxins in the blood such as drugs into inactive metabolites [13]. Hepatotoxicity could be recognized by elevated liver function tests [7, 14]. Is any elevation in liver function tests upon receiving Anthracyclines (first dose) considered hepatotoxicity?

This study aims to examine the pattern of hepatotoxicity in cancer patients upon receiving the first dose of Anthracyclines at KAUH. Some 50 cancer patients'

clinical-pathological data and their preselected lab results (AST, ALT, ALP, and T.Bil) were collected to accomplish this aim. The study statistical analysis was performed and conveyed that the ALT and T.Bil were the only parameters that provided statistical significance difference. Their *p-values* were 0.001 and 0.012 respectively. AST results provided a borderline significance difference with a *p-value of* 0.07. ALP results showed no significant difference with *the p-value* 0.405. Additionally, because of the availability of TP, ALB and GGT results, their *p-values* were calculated. Both TP and ALB results revealed no significant difference *with p-values* of 0.132 and 0.131. Interestingly, GGT results displayed a significant difference with a *p-value* of 0.012. The previous paragraph results could be used to examine the study's research hypothesis. The research hypothesis stated the following; the liver function tests (ALT, AST, ALP, and T.Bil) are increased after receiving the first dose of anthracyclines in cancer patients. According to the study results, the research hypothesis was not met in our study, even with both ALT and T.Bil providing significance *p-values*. While the ALT results were significantly increased, in contrary, the T.Bil results were significantly decreased. Additionally, the other preselected liver function tests (AST and ALP) failed to provide significant *p-values*. On the other hand, with consideration to the borderline significance of AST (0.07), it is possible to state that the research hypothesis was partially met in our study. The following paragraphs will discuss the theoretical and results in parts of this study.

To answer the previous question, the National Cancer Institute (NCI) has classified hepatotoxicity grades into five grades according to the elevation of serum enzymes' activities. These serum enzymes are ALT, AST, ALP, and GGT. Grade 1 (mild) if enzymes levels are > ULN (upper limits of normal) up to 2.5x ULN. Grade 2 (moderate) if these levels are > 2.5x to 5x ULN. Grade 3 (severe) if their levels are > 5x to 20x ULN; and grade 4 (life-threatening) if enzymes levels are > 20x ULN. Grade 5 (fatal) with no definition. Similarly, serum bilirubin concentration has been graded as (mild) if > ULN to 1.5x ULN, (moderate) if > 1.5 to 3x ULN, (sever) if > 3 to 8x ULN, and (life-threatening) if > 8x ULN [7]. Another grading system was crafted by The Drug-Induced Liver Injury Network (DILIN) and classified liver injury according to clinical measurements instead of laboratory values. Therefore, lab results were just used in the first two grades; Grade 1 (mild) in patients with an elevation of ALT and or ALP. Grade 2 (moderate) in case of elevated bilirubin and coagulopathy [7, 8]. Applying the previous grading systems to our results will provide an insightful understanding of our study.

Serum AST and ALT activities were used as markers of liver damage. Regarding the results of aminotransferases (AST and ALT), theoretically, they should be elevated upon receiving Anthracyclines that have known hepatotoxicity [7]. The reason behind it is the fact that any liver injury, acute or chronic, consequently, leads to an increase in serum concentrations of AST and ALT [14]. AST results in our study reflected an elevation upon receiving Anthracyclines. The mean of AST results in the pre-anthracyclines to post-anthracyclines data was reported to be 25.1(IU/L) and 29.7 (IU/L). Even with this increase (from 25.1 to 29.7), the mean (post-anthracyclines) is still under the upper limit of the AST normal range (15-37 IU/L). Therefore, applying the NCI grading system, this result doesn't indicate hepatotoxicity. Another way to scrutinize the elevation of AST results is by using the Wilcoxon signed-rank test. The gained p-value was unexpected because it indicated borderline to no significant increase between the pre-anthracyclines and post-anthracyclines results (p=0.07927). This might be due to the small sample size of our study. The research on the topic of AST and anthracyclines revealed inconsistent outcomes. Our results are similar to the results of a study performed by Amin *et al.* [15]. They could not find a significant increase between the pre-anthracyclines and post-anthracyclines AST results. On the other hand, Damodar*et al.* study found a statistically significant increase in AST results with a p-value < 0.001 [16]. Blood-based measurement of AST and ALT was described as a useful tool to evaluate hepatocellular carcinoma prognosis. Recently, some researchers have applied AST/ALT as a significant prognostic factor in patients with non-metastatic cell carcinoma [17, 18]. Some studies showed that cancer cell proliferation could also obtain energy through glutamine metabolism, which is necessary for tumor cells to maintain nucleotide biosynthesis and non-essential amino acids, which are catalyzed by AST and ALT. ALT results in this study were elevated upon receiving anthracyclines. These results were predicted, because of the known hepatotoxicity anthracyclines and the ALT high specificity to the liver [7, 14]. The mean of ALT results in the pre- anthracyclines to post-anthracyclines data was observed to be 30.6 (IU/L) and 37 (IU/L). Applying the NCI grading system, even with the post mean elevation from 30.6IU/L to 37IU/L, it is still under the upper limit of ALT normal range (31-61 IU/L). Consequently, ALT results do not indicate hepatotoxicity. The elevation of ALT results was examined and demonstrated a clear statistically significant increase between the pre-anthracyclines and post-anthracyclines sets of data (p=0.00097). Our results are following the study done by Damodar*et al.,* 2014. Their study displayed a statistically significant elevation in the ALT results after receiving

anthracyclines with a p-value < 0.001 [16]. Serum ALP is a ubiquitous enzyme present in all tissues but is mainly concentrated in the liver, kidney, placenta, and bone [11], and has been used to monitor primary bone lesions.ALP results in this study displayed no elevation after receiving anthracyclines. These results are confronting the nature of the relationship between ALP and liver injury. ALP secreted from the liver; therefore, any liver injury could increase the blood level of ALP [17]. As a result, adding the known hepatotoxicity of anthracyclines [7], ALP should theoretically be elevated. In contrast, the mean of ALP results in the pre- anthracyclines to post-anthracyclines data was almost identical (89.4 IU/L and 89.1IU/L). Furthermore, ALP results displayed no statistical significance difference between the pre- and post- readings (p=0.40517). In contrary to our results, Alshabanah*et al.,* results presented significant of ALP upon receiving anthracyclines [19]. Total bilirubin (T-Bil), is cleared from the blood, treated, and then, secreted into the bile by the liver. Therefore, any liver damage will decrease the liver's ability to uptake T.Bil from the blood. Consequently, the impaired uptake ability of the liver will lead to an elevation of the T.Bil level in the blood [17]. Theoretically, T.Bil should increase upon receiving anthracyclines. In contrast, our results presented a reduction of the T.Bil level after receiving anthracyclines. The mean of T.Bil results in the pre- anthracyclines to post-anthracyclines data was observed to be 6.2 µmol/L and 5.3µmol/L. Moreover, T.Bil results presented a statistical significant decrease between the pre and post readings (p=0.01911). This questionable result might be caused by many factors such as; the study design (retrospective), random errors and study small size. Following our results, Boulin et al. found no elevation in TBil level after receiving anthracyclines(Boulin et al., 2014). In contrary, Damodar et al. results revealed a significant elevation in T.Bil with a p-value= 0.03 [16].

After discussing the preselected analytes in our study (ALT, AST, ALP, and T.Bil), analyzing the remaining data (GGT, TP, and ALB) could reveal interesting findings. Since GGT found in high concentrations in the liver, it is expected to be elevated in case of any liver injury [20]. Therefore, supposedly, GGT should increase upon receiving anthracyclines, because of the anthracyclines' hepatotoxicity [5]. This was supported by our GGT results. GGT results illustrated a statistically significant increase between the pre-anthracyclines and post-anthracyclines data with a p-value = 0.01222. Additionally, the mean of GGT results in the pre-anthracyclines to post-anthracyclines data was documented to be 33.3 (IU/L) and 41.7 (IU/L). Applying the NCI grading system, regardless of the elevation of the post mean (41.7 IU/L), the post means is still lower than the upper limit of the GGT normal range (5-85 IU/L). As a result, GGT results don't indicate hepatotoxicity. In agreement with our results, Morsi et al results revealed a significant elevation in post-anthracyclines GGT results [21].

In the case of liver injury, the TP level in the blood will decrease [22]. Therefore, knowing the hepatotoxic effect of anthracyclines, it is anticipated that the TP level will decrease upon receiving anthracyclines. On the other hand, our TP results reported no statistical significance decrease between the pre-anthracyclines and post-anthracyclines data (p=0.13252). Contrary to our results, Saleem et al. reported a significant drop in TP results after receiving anthracyclines with a p-value <0.05 [23].

ALB is the main protein in the blood and it is formed by the liver [17]. In the presence of liver injury, the ALB level in the blood will decrease [22]. Based on this, it is expected to be deceased upon receiving anthracyclines. In contrast, ALB results in our study revealed no statistically significant decrease between the pre-anthracyclines and post-anthracyclines data (p=0.13136). supporting our results, Saleem *et al*. study found no significant decrease in ALB results upon receiving anthracyclines with a p-value >0.05 [23].

All over our discussion, the variation among the results about the topic of anthracyclines and liver function tests was clear. This reflects the difficulty of obtaining practical (research) results that match the theoretical data in the research field. In this study, theoretically, the preselected liver function tests (AST, ALT, ALP, and T.Bil) should be elevated upon receiving anthracyclines. Based on several studies in our paper, this is difficult to obtain practically. The differences between the studies' findings could be explained by the variation in their methodologies, samples' sizes, patients' baseline characteristics (pre-existing conditions). This study had two limitations. The first limitation was the small sample size. This could impair the study statistical validity because it affects the sample power. Second, the retrospective design of the study. This limitation negatively impacted the availability of samples'laboratory and clinic-pathological data. The absence of proper documentation is one of the challenging tasks in this research and led to many missing results that could increase the validity and quality of our statistics.

CONCLUSION

Although our results suggest that ALT, AST, and GGT are elevated upon receiving the first dose of anthracyclines, their elevation doesn't indicate hepatotoxicity. Thus, we failed to reject the null hypothesis and conclude that the liver function tests (ALT, AST, ALP, and T.Bil) are not increased after

receiving the first dose of anthracyclines in cancer patients.

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