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Safety of Anthracyclines in Breast Cancer Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

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ABSTRACT

Objective: To examine the safety of doxorubicin and epirubicin in breast cancer patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Material and Methods: A retrospective cohort study was conducted at a single oncology center. Patients with breast cancer and G6PD deficiency, who received doxorubicin cyclophosphamide (AC) or epirubicin cyclophosphamide (EC) chemotherapy, were included. Control cohorts included breast cancer patients with normal G6PD activity matched in a 1:1 ratio based on age, gender, and treatment (AC or EC).

Results: A total of 94 breast cancer patients were included, consisting of 47 G6PD-deficient patients and 47 patients in the control cohort. Among the G6PD-deficient group, 22 women received AC chemotherapy; 25 patients, comprising 24 women and one man, were treated with EC. Matched control cohorts included 22 patients for AC and 25 for EC. G6PD-deficient patients underwent a total of 85 cycles of AC and 98 cycles of EC. No case of acute hemolysis was reported. Median changes in hemoglobin and bilirubin levels from baseline at weeks 3, 6, and 9 revealed no significant differences between the G6PD-deficient and control cohorts for both AC and EC treatments. There was no significant correlation between G6PD enzyme activity and changes from baseline hemoglobin levels at week 3 in the AC [$r_s(42)=-0.07$, $p=0.65$] and EC [$r_s(48)=0.11$, $p=0.45$] cohorts.

Conclusion: These findings support the safety of doxorubicin and epirubicin for treating breast cancer patients with G6PD deficiency.

Keywords: G6PD deficiency; hemolysis; anthracycline; epirubicin; doxorubicin; breast neoplasms

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent enzymopathy of red blood cells, affecting over 500 million individuals worldwide. This X-linked hereditary enzyme deficiency compromises erythrocytes' ability to resist oxidative stress. Consequently, affected individuals may experience episodes of acute hemolytic anemia when exposed to increased oxidant stress. Common triggers of acute hemolytic anemia include consuming fava beans, exposure to certain drugs, and infection.[1] Mutations in the *G6PD* gene give rise to various functional variants of G6PD. Currently, more than two hundred G6PD variants have been identified, some of which exhibit reduced G6PD activity.[2] The risk of acute hemolytic anemia is linked to the residual activity of the G6PD enzyme. According to the World Health Organization classification, G6PD variants exhibiting a median residual enzyme activity of 60% or higher are classified as normal and do not pose a risk of hemolysis.[1,3] The prevalence of G6PD deficiency varies significantly among different populations. It is particularly common in specific geographical areas, including the Middle East, the Mediterranean, certain parts of Africa, and Southeast Asia.[3]

Anthracyclines, a class of chemotherapeutic agents, are extensively utilized in the treatment of various cancers, including breast cancer and lymphomas. Nevertheless, the existing literature on the safety of anthracyclines in G6PD

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deficiency is extremely limited. *In vitro* studies indicate that doxorubicin may precipitate significant oxidative damage in G6PD-deficient red blood cells, potentially resulting in hemolysis.[4] Moreover, doxorubicin was reported to be a suspected trigger of hemolysis in a patient with cancer and G6PD deficiency.[5] Clinicians require more robust data to effectively inform their decision-making regarding the use of anthracyclines in the treatment of cancer patients with G6PD deficiency, particularly in areas where G6PD deficiency is prevalent. Consequently, this study was designed to assess the safety of administering doxorubicin and epirubicin to breast cancer patients with G6PD deficiency.

MATERIAL AND METHODS

Study Design and Setting

This retrospective matched cohort study aimed to evaluate the safety of anthracycline administration in breast cancer patients with G6PD deficiency. The study was conducted in the medical oncology department of the Bahrain Oncology Center, which serves as the primary oncology facility providing care to the majority of cancer patients in the Kingdom of Bahrain. The prevalence of G6PD deficiency is notably high in Bahrain, with a reported rate of 22.3%.[6] Due to this high prevalence, G6PD enzyme activity is routinely measured in all patients before commencing chemotherapy. The study was approved by the institutional review board of King Hamad University Hospital (approval number: 21-407, date: 21.03.2021). The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[7]

Study Population

Clinical data were obtained from hospital electronic medical records. All patients who were assessed in the medical oncology clinic between April 2018 and December 2022, and underwent testing for G6PD enzyme activity were assessed for eligibility. Patients were eligible if they were over 18 years of age, diagnosed with breast cancer, and had received chemotherapy containing either doxorubicin or epirubicin. Patients were excluded if they were diagnosed with hematological malignancies, sickle-cell disease, or hemolytic anemias resulting from causes other than G6PD-related hemolysis, or if follow-up data after administration of chemotherapy were unavailable. Control cohorts were selected from the same patient population with normal G6PD activity levels and matched in a proportion of 1:1 based on the type of anthracycline administered (doxorubicin or epirubicin), age (±5 years), and gender. All patients received anthracyclines in combination with cyclophosphamide as either standard dose doxorubicin cyclophosphamide (AC) regimen (i.e., doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, 3-weekly cycles) or epirubicin cyclophosphamide (EC) regimen (i.e., epirubicin 75 or 90 mg/m^2 and cyclophosphamide 600 mg/m^2, 3-weekly cycles). Four cohorts were established as follows: 1 - G6PD-deficient patients treated with AC regimen (G6PD-deficient AC cohort); 2 - control cohort including patients with normal G6PD activity treated with AC regimen (control AC cohort); 3 - G6PD-deficient patients treated with EC (G6PD-deficient EC cohort); and 4 - control cohort including patients with normal G6PD activity treated with EC regimen (control EC cohort).

Data Sources and Assessments

The quantitative measurement of G6PD enzyme activity was performed on whole blood samples of the patients using an automated UV-based enzymatic assay (Mindray BS 240 chemistry analyzer, People's Republic of China). The reaction principle relied on the measurement of the absorbance change at 340 nm resulting from the reduction of NADP by the G6PD enzyme in the presence of glucose-6 phosphate.[8] The results were reported in units per gram of hemoglobin [U/g hemoglobin (Hb)]. G6PD activity levels below 6.72 U/g Hb were classified as G6PD-deficient, corresponding to G6PD activity of 60%, based on an adjusted male median level of 11.2 U/g Hb.

The primary outcome variable was the incidence of acute hemolytic anemia following chemotherapy cycles. We assessed the occurrence of acute hemolytic anemia by reviewing clinic visit notes, emergency room visit notes, and laboratory results. Considering that mild cases of hemolysis may remain undiagnosed, we reviewed the hemoglobin and total bilirubin levels, which were routinely assessed before each chemotherapy cycle.[2] We recorded the hemoglobin and total bilirubin levels at baseline, week 3, week 6, and week 9. These time points were selected because doxorubicin and epirubicin are most frequently administered every 3 weeks. In cases of multiple measurements, the lowest hemoglobin level and the highest bilirubin level within the 3-week intervals were recorded. Data on blood transfusions during the chemotherapy cycles and three weeks after the last chemotherapy cycle were also collected. The frequencies of hematologic adverse events, including anemia, leucopenia, neutropenia, and thrombocytopenia, during the chemotherapy cycles and within three weeks after the last chemotherapy cycle, were recorded and graded based on the Common Terminology Criteria for Adverse Events version 5.0. Data on blood transfusions during the same periods were also documented.

Statistical Analysis

The discrete variables were reported as numbers and percentages, and continuous variables were reported as medians and ranges or interquartile ranges. Comparisons between cohorts were performed using the chi-square test or Fisher's exact test for discrete variables and the Wilcoxon rank sum test for continuous variables. Spearman's rank correlation method was utilized to evaluate the correlation between G6PD enzyme activity and change from the baseline hemoglobin level, at week 3. A p-value less than 0.05 was considered statistically significant. The statistical analyses were performed using STATA software (version 14; Stata Corporation, College Station, TX, USA). Missing data were not imputed in this study. In cases where data were missing, we performed complete case analysis by excluding observations with missing values from the analyses.

RESULTS

A total of 1,974 individuals who underwent G6PD enzyme activity testing in a medical oncology clinic were evaluated for eligibility. Out of these, 419 (21.2%) were found to have G6PD deficiency. Fifty breast cancer patients who underwent treatment with anthracyclines were identified. Two patients with insufficient follow-up data and one patient with sickle-cell disease were excluded from the study. In total, 47 patients with breast cancer and G6PD deficiency who had received either AC (22 patients) or EC (25 patients) regimens in the control cohorts were included, along with 47 patients in the control cohorts (22 treated with AC and 25 treated with EC).

The clinical characteristics of the G6PD-deficient and control cohorts are summarized in Table 1. Among G6PD-deficient patients, all were women in the AC cohort, while only one patient was male in the EC cohort. The median age of patients in the G6PD-deficient AC and EC cohorts was 51.6 (range 29.7-62.8) and 45.3 (range 33.4-64.2) years, respectively. The median G6PD activity was 2.3 U/g Hb in the G6PD-deficient AC and 0.88 U/g Hb in the G6PD-deficient EC cohorts. The majority of G6PD-deficient patients (91% in the AC cohort and 88% in the EC cohort) received anthracyclines as adjuvant or neoadjuvant chemotherapy for early-stage breast carcinoma.

Safety of Doxorubicin

The G6PD-deficient AC cohort included 22 patients. A total of 85 cycles of AC chemotherapy (median 4, range 1 to 6 cycles) were administered. No cases of acute hemolytic anemia were detected in the G6PD-deficient AC cohort.

The median changes from baseline hemoglobin levels at weeks 3, 6, and 9 were -0.5 (range -2.3, 1), -0.6 (range -2.6, 0.2), and -0.4 g/dL (range -3, 0.3), respectively (Figure 1). The median changes in total bilirubin levels at weeks 3, 6, and 9 were -2.9 umol/L (range -12.1, 1.2), -2.7 umol/L (range -12.8, 1), and -3.4 umol/L (range -14, 0.8), respectively. There was no significant difference in the changes from baseline hemoglobin and bilirubin levels between the G6PD-deficient and control AC cohorts (Table 2). No significant correlation was observed between G6PD activity and change from the baseline hemoglobin level at week 3 [$r_s(42)$=-0.07, p=0.65] (Figure 2).

The frequencies of anemia, leucopenia, and neutropenia are provided in Table 3. Grade 1 or 2 anemia was observed in 86.4% and 77.3% of the G6PD-deficient and control cohorts, respectively. One patient in the G6PD-deficient cohort and one patient in the control cohort had grade 3 anemia. No significant differences were detected in frequencies of anemia, leucopenia, and neutropenia between G6PD-deficient and control cohorts. The number of patients who received red blood cell transfusions was not significantly different between G6PD-deficient and control cohorts.

Safety of Epirubicin

The G6PD-deficient EC cohort included 25 patients. A total of 98 cycles of EC chemotherapy (median 4, range 1 to 6 cycles) were administered. No cases of acute hemolytic anemia were detected in the G6PD-deficient EC cohort.

The median changes in hemoglobin levels at weeks 3, 6, and 9 from baseline were -0.7 (range 2.5 to 0.4), -1.0 (range -3.1 to 0.8), and 0.8 g/dL (range -2.9 to 1), respectively. The median changes in total bilirubin levels at weeks 3, 6, and 9 were -1.9 (range -24.5, 5.3), -3.0 (range -21, 1.1), and -2.9 (range -23.9, 3.5) umol/L, respectively (Figure 1). There was no significant difference in the changes from baseline hemoglobin and bilirubin levels between the G6PD-deficient and control EC groups (Table 2). No significant correlation was observed between G6PD activity and change from the baseline hemoglobin level at week 3 [$r_s(48)$=-0.11, p=0.45] (Figure 2).

Grade 1 or 2 anemia was observed in 84% and 72% of the G6PD-deficient and control cohorts, respectively (Table 3). One patient in the G6PD-deficient cohort and three patients in the control cohort had grade 3 anemia. No significant differences were detected in frequencies of anemia, leucopenia, and neutropenia between G6PD-deficient and control cohorts. The number of patients who received red blood cell transfusions were not significantly different between G6PD-deficient and control cohorts.

DISCUSSION

To the best of our knowledge, this is the first cohort study exploring the safety of doxorubicin and epirubicin in patients

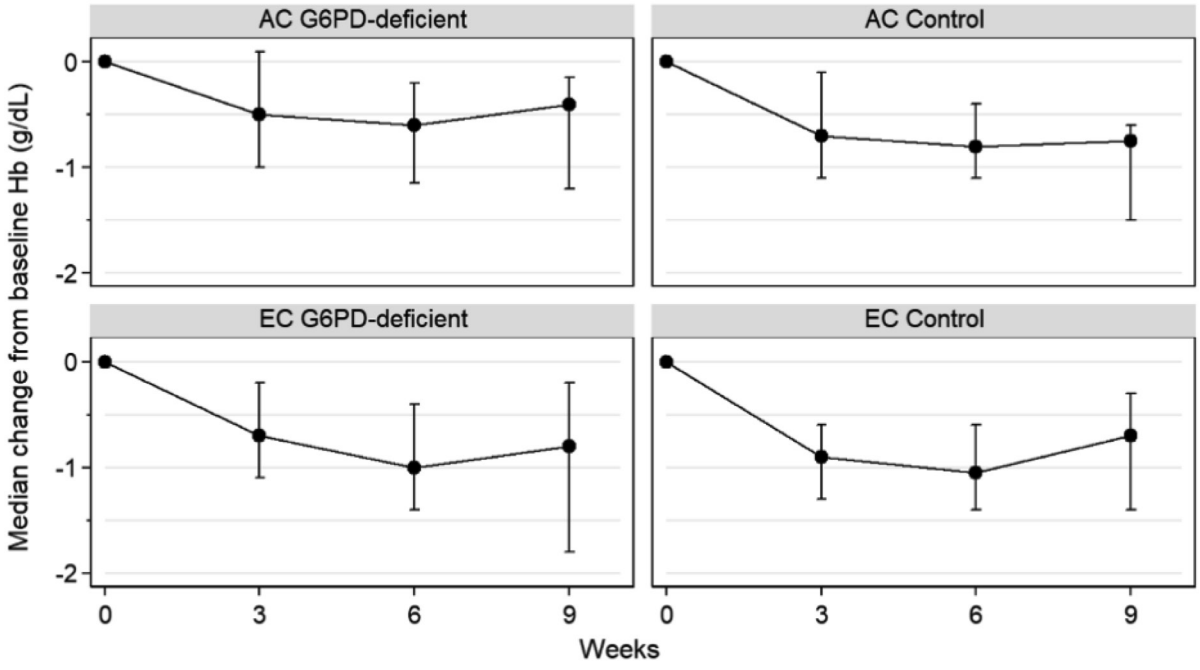

FIGURE 1: Median changes in hemoglobin levels from baseline across patient cohorts. Error bars are representing the 25th and 75th percentile values.

AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; Hb: Hemoglobin.

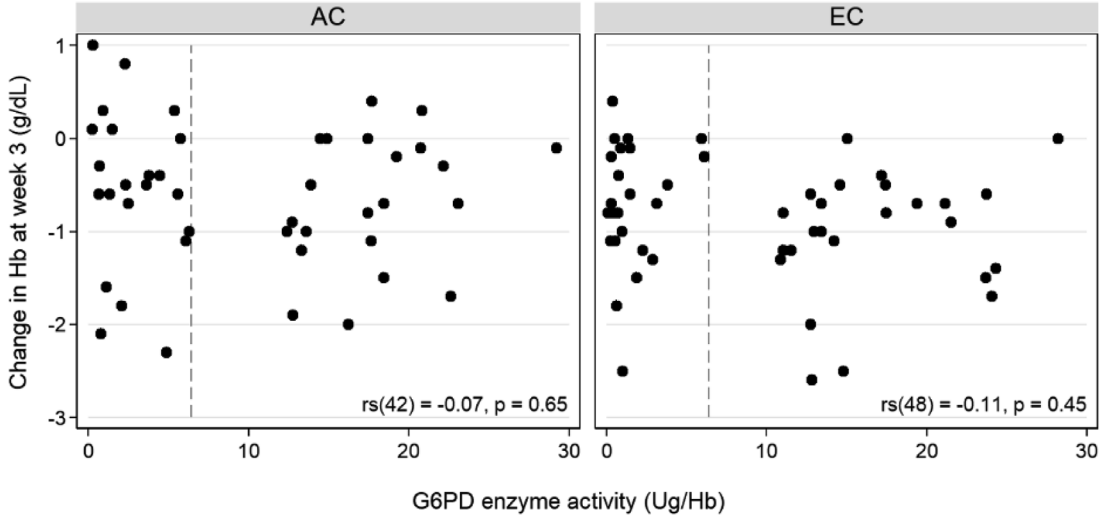

FIGURE 2: The scatter plots illustrate the change in hemoglobin levels at week 3 compared to baseline. Reference lines indicate a cutoff G6PD activity level of 6.72 U/g Hb, corresponding to G6PD activity of 60%.

AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; Hb: Hemoglobin.

with breast cancer and G6PD deficiency. We did not observe any cases of acute hemolytic anemia in this patient population after doxorubicin or epirubicin treatment. To further explore the possibility of mild hemolysis without generating clinical symptoms, we assessed additional parameters. The changes in hemoglobin and total bilirubin levels after doxorubicin and epirubicin administration, were similar between G6PD-deficient and control cohorts. Hence, the occurrence of clinically silent mild hemolysis is unlikely. Furthermore, there was no correlation between G6PD enzyme activity and the decrease in the hemoglobin levels from baseline in both doxorubicin and epirubicin groups. The frequencies of blood transfusions were similar between G6PD-deficient and control cohorts. Overall, our results did not indicate an increased

TABLE 1: Baseline characteristics of the study population.

		AC cohorts		EC cohorts	
		G6PD-deficient	Control	G6PD-deficient	Control
n		22	22	25	25
Age, median (range)		51.6 (29.7-62.8)	51.9 (24.5-63.5)	45.3 (33.4-64.2)	45.5 (30.6-68.7)
Gender, n (%)					
	Female	22 (100)	22 (100)	24 (96)	24 (96)
	Male	0	0	1 (4)	1 (4)
Breast cancer stage, n (%)					
	I-II	7 (31.8)	12 (54.5)	5 (20)	10 (40)
	III	13 (59.1)	8 (36.4)	17 (68)	11 (44)
	IV	2 (9.1)	2 (9.1)	3 (12)	4 (16)
Treatment setting, n (%)					
	Neoadjuvant	12 (54.5)	14 (63.6)	10 (40)	11 (44)
	Adjuvant	8 (36.4)	6 (27.3)	12 (48)	10 (40)
	Metastatic	2 (9.1)	2 (9.1)	3 (12)	4 (16)
Histology					
	IDC	18 (81.8)	19 (86.4)	23 (92)	24 (96)
	ILC	4 (18.2)	3 (13.6)	2 (8)	1 (4)
IHC profile					
	HR-positive	15 (68.2)	16 (72.7)	18 (72)	19 (76)
	HER2-positive	7 (31.8)	3 (13.6)	3 (12)	5 (20)
	Triple-negative	5 (22.7)	3 (13.6)	5 (20)	4 (16)
G6PD activity (U/g Hb), median (range)		2.3 (0.2-6.3)	17.5 (12.4-29.2)	0.88 (0.1-6.1)	14.8 (10.9-28.2)
Total anthracycline cycles		85	85	98	91
No. of anthracycline cycles, median (range)		4 (1-6)	4 (3-4)	4 (1-6)	4 (1-4)

AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; Hb: Hemoglobin; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; IDC: Invasive ductal carcinoma; IHC: Immunohistochemistry; ILC: Invasive lobular carcinoma.

risk of hemolysis in breast cancer patients with G6PD deficiency treated with AC and EC regimens. These findings do not support routine screening for G6PD deficiency prior to administering anthracycline-containing chemotherapy to breast cancer patients in populations where G6PD deficiency is highly prevalent of G6PD deficiency.

We observed a high frequency of anemia in our patient population while receiving AC and EC chemotherapy regimens. More than 80% of the patients were reported to have anemia in all cohorts, although most cases of anemia were grade 1 or 2. The high frequencies of grade 1 and 2 anemia during chemotherapy were possibly related to prevalent baseline anemia. In the general population of Bahrain, anemia is common, with a reported prevalence of 36% among healthy females aged 15 to 49, primarily due to the high prevalence of iron deficiency and thalassemia trait.[9-11] Anemia is a common adverse effect of AC and EC chemotherapy regimens, with reported prevalence rates varying from 40% to 90% among different populations.[12,13] However, grade 3 anemia (i.e., hemoglobin level of less than 8 g/dL) is less frequently observed with AC and EC regimens. The frequency of grade 3 or 4 anemia was reported in 1% to 4% with the AC regimen, and 1% to 6.3% with the EC regimen.[12-15] Among patients with G6PD deficiency, we observed grade 3 anemia in one patient (4.6%) in the AC cohort and one patient (4%) in the EC cohort. Notably, the frequencies of anemia were similar among G6PD-deficient and control cohorts.

Based on the available literature, there has been a single reported instance of potential acute hemolysis following the administration of doxorubicin in a patient with G6PD deficiency, dating back to 1984. This was a 58-year-old Afro-American male who was treated with doxorubicin for metastatic sarcoma. Three days after the administration of doxorubicin, his hemoglobin level had decreased from 14.8 g/dL to 10.6 g/dL, along with hemoglobinemia,

TABLE 2: Changes in hemoglobin and bilirubin levels from baseline in G6PD-deficient and control cohorts.

			G6PD-deficient		Control		
		n1/n2[a]	Level	Change from baseline	Level	Change from baseline	p-value[b]
AC							
Hemoglobin (g/dL)	**Baseline**	22/22	12.2 (8.9, 14.7)		12.2 (10.3, 13.9)		
	Week 3	22/22	11.6 (7.9, 14.2)	-0.5 (-2.3, 1)	11.7 (8.8, 13.3)	-0.7 (-2, 0.4)	0.48
	Week 6	20/22	11.4 (9.9, 13.1)	-0.6 (-2.6, 0.2)	11.4 (8.8, 13.5)	-0.8 (-3.9, 0.5)	0.49
	Week 9	20/22	11.3 (9.6, 12.6)	-0.4 (-3, 0.3)	11.0 (7.5, 13.4)	-0.8 (-5.2, -0.2)	0.06
Total bilirubin (umol/L)	**Baseline**	22/22	7.9 (3.7, 24)		6.6 (4.2, 32)		
	Week 3	19/21	5.1 (2.8, 8.9)	-2.9 (-12.1, 1.2)	4.9 (3, 20.1)	-2.0 (-16, 2)	0.67
	Week 6	17/22	5.7 (2.1, 11.9)	-2.7 (-12.8, 1)	4.6 (3, 21)	-1.7 (-19, -0.4)	0.20
	Week 9	19/22	4.8 (2.1, 10)	-3.4 (-14, 0.8)	5.3 (3, 20.6)	-1.3 (-17, 1.5)	0.13
EC							
Hemoglobin (g/dL)	**Baseline**	25/25	11.4 (8.4, 13.7)		12.2 (8.1, 14)		
	Week 3	25/25	11.2 (8.4, 12.4)	-0.7 (-2.5, 0.4)	11.1 (6.4, 13)	-0.9 (-2.6, 0)	0.12
	Week 6	23/24	10.8 (7, 12.8)	-1.0 (-3.1, 0.8)	11.0 (6.7, 13.7)	-1.0 (-3.5, 0.9)	0.70
	Week 9	23/20	10.8 (8.2, 12.6)	-0.8 (-2.9, 1)	11.3 (9.9, 12.7)	-0.7 (-2.2, 0.9)	0.63
Total bilirubin (umol/L)	**Baseline**	25/25	8.3 (3, 31.9)		7.9 (4.4, 21)		
	Week 3	22/25	5.9 (2.5, 15.9)	-1.9 (-24.5, 5.3)	5.7 (3, 35)	-1.2 (-9.8, 14)	0.22
	Week 6	23/22	5.0 (2.8, 12)	-3.0 (-21, 1.1)	5.1 (3, 11.1)	-1.6 (-9.9, 0.1)	0.18
	Week 9	23/21	5.1 (2.4, 10.7)	-2.9 (-23.9, 3.5)	5.8 (3, 11.8)	-1.5 (-9.3, 4)	0.13

Reported are median values with corresponding ranges in parentheses. a n1/n2 indicates the number of patients in the G6PD-deficient and control cohorts, respectively. b P-values were derived from the Wilcoxon rank sum test, which compared changes from baseline levels between G6PD-deficient and control cohorts. AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase.

hemoglobinuria, elevated reticulocytes, and Heinz bodies in the peripheral smear. This report presents a potential link between the use of doxorubicin and acute hemolysis in individuals with G6PD deficiency. Nonetheless, this connection has not been corroborated by other studies. Considering the high incidence of breast cancer and G6PD deficiency, particularly in specific geographic regions, it is reasonable to anticipate a greater frequency of cases of hemolysis following anthracycline administration if a causal relationship exists. Chung et al.[16] reported the safe administration of AC the chemotherapy in a female with G6PD deficiency. Additionally, a case series reported from Italy involving 40 G6PD-deficient patients showed no hemolytic events with the use of epirubicin-containing chemotherapy regimens.[17] In a separate study, daunorubicin, another anthracycline, was evaluated for safety in 22 pediatric patients diagnosed with G6PD deficiency and acute leukemia, and was found to be safe.[18]

Study Limitations

The present study is subject to limitations that should be acknowledged. The study population consisted mainly of females, with only one G6PD-deficient male patient included. As such, caution is warranted in extrapolating the results to males with G6PD deficiency. Secondly, this study has a retrospective observational design, which poses inherent limitations. The laboratory assessments were performed routinely before the 3-weekly chemotherapy cycles or as clinically indicated between the cycles. However, closer monitoring of hemoglobin levels along with hemolysis markers could have provided more comprehensive information. Nonetheless, all emergency department and hospital visits were thoroughly reviewed. It should be noted that our institution is the primary oncology center in Bahrain, and all cases are referred to our center in the event of an emergency. Therefore, it is improbable that a symptomatic hemolytic episode would remain unnoticed. Finally, we were unable to obtain

TABLE 3: Frequencies of hematological toxicities.

		G6PD-deficient	Control	p-value
AC		**n=22**	**n=22**	
Anemia	Grade 1	15 (68.2)	16 (72.7)	0.48
	Grade 2	4 (18.2)	1 (4.6)	
	Grade 3	1 (4.6)	1 (4.6)	
Leucopenia	Grade 1-2	12 (54.6)	11 (50)	0.77
	Grade 3-4	6 (27.3)	5 (22.7)	
Neutropenia	Grade 1-2	7 (31.8)	3 (13.6)	0.27
	Grade 3-4	9 (40.9)	9 (40.9)	
RBC transfusions*		2 (9.1)	1 (4.6)	0.55
EC		**n=25**	**n=25**	
Anemia	Grade 1	14 (56)	15 (60)	0.43
	Grade 2	7 (28)	3 (12)	
	Grade 3	1 (4)	3 (12)	
Leucopenia	Grade 1-2	12 (48)	7 (28)	0.16
	Grade 3-4	8 (32)	7 (28)	
Neutropenia	Grade 1-2	7 (28)	3 (12)	0.10
	Grade 3-4	12 (48)	9 (36)	
RBC transfusions*		1 (4)	2 (8)	0.55

* The number of patients who received at least one RBC transfusion is reported. AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; RBC: Red blood cell.

genotypic data on G6PD variants, as well as the proportion of homozygous and heterozygous female patients within our patient cohort. Of note, the G6PD Mediterranean variant is the most frequent among G6PD-deficient individuals in Bahrain, accounting for 91-95% of the cases as indicated by prior studies.[19,20]

CONCLUSION

The results of this study support the safety of doxorubicin and epirubicin in G6PD-deficient cancer patients. Our study contributes to the limited literature on this topic and may inform clinical decision-making in the management of G6PD deficient patients with cancer.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board, King Hamad University Hospital (approval number: 21-407, date: 21.03.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: Z.S., Ç.P.Ö., Design: Z.S., Ç.P.Ö., Data Collection or Processing: Z.S., N.M.A., F.F., F.Ö., Ç.P.Ö., Analysis or Interpretation: Z.S., N.M.A., F.F., F.Ö., Ç.P.Ö., Literature Search: Z.S., Writing: Z.S., N.M.A., F.F., F.Ö., Ç.P.Ö.

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