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Toxicity profile of Doxorubicin-Cyclophosphamide and Doxorubicin-Cyclophosphamide followed by Paclitaxel regimen and its associated factors among women with breast cancer in Ethiopia: A prospective cohort study

Diriba Alemayehu Gadisa[1], Mathewos Assefa[2], Shu-Hua Wang[3,4] and Getnet Yimer[5]

Abstract

Background: Management of patients with breast cancer undergoing chemotherapy is complicated by a very high rate of adverse drug reactions which is even more challenging in developing countries like Ethiopia where the toxicity profile of chemotherapy is lacking. The present study aimed at evaluating the toxicity profile of Doxorubicin-Cyclophosphamide (AC) and Doxorubicin-Cyclophosphamide→Paclitaxel (AC→T) regimens among 146 patients with breast cancer in Ethiopia.

Methods: This prospective cohort study, with the median of six months' follow-up, was conducted from January 1 to September 30, 2017 GC at the only nationwide oncology center, Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia. Seventy-one patients received AC, while 75 received AC-T regimen. The toxicity with the highest grade during any cycle was considered as the toxicity grade for that patient. SPSS version 22 was used for analysis.

Results: The overall frequent non-hematological adverse drug reactions reported for both regimens were fatigue 144 (98.7%), dysgeusia 142 (97.3%), skin hyperpigmentation 141 (96.6%), nausea 136 (93.2%), vomiting 129 (88.4%), gastritis 122 (83.6%), peripheral neuropathy 108 (74%), and myalgia/arthralgia 110 (75.3%). Neutropenia 107 (73.3%), leukopenia 102 (69.9%), and anemia 51 (34.9%) were the most frequent overall grade hematological toxicities reported. However, those received AC regimen suffered more from grade 2 and above leukopenia (35.2% vs. 17.3%, $P = 0.014$), anemia (16.9% vs. 2.7%, $P = 0.004$), and alkaline phosphatase increment (11.3% vs. 2.7%, $P = 0.039$) than AC-T regimen. On the contrary, those received AC-T regimen suffered more from severe arthralgia/myalgia (2.8% vs. 2%, $P = 0.001$), peripheral neuropathy (1.4% vs. 36%, $P = 0.000$), and gastritis (14.1% vs. 29.3%, $P = 0.026$) than AC regimen. Pretreatment blood cell counts, having stage IV breast tumor, older age, and lower body surface area were significant predictors of grade 2 to above hematological toxicities. Older age, arthralgia/myalgia, and skin hyperpigmentation occurred during the cohort were significant predictors of grade 2 to above oral mucositis, peripheral neuropathy, and fatigue, respectively.

Conclusion: Patients who received the AC regimen suffered more from hematological abnormalities, while those on the AC-T regimen experienced more of non-hematological toxicities. Overall, we report high incidences of AC and AC-T regimens-induced toxicities in Ethiopian women with breast cancer, and they may require prior support based on pretreatment blood counts, age and body surface area, and close follow-up during chemotherapy.

[1]Pharmacy Department, College of Medicine and Health Sciences, Ambo University, Ambo, Ethiopia
[2]School of Medicine, College of Health Sciences, Radiotherapy Center, Addis Ababa University, Addis Ababa, Ethiopia
[3]Division of Infectious Diseases, Department of Internal Medicine Medical, Ohio State University, Columbus, OH, USA
[4]Ben Franklin TB Control Program, Ohio State University, Columbus, OH, USA
[5]Ohio State Global One Health Initiative, Office of International Affairs, The Ohio State University, Addis Ababa, Ethiopia

Corresponding author:
Diriba Alemayehu Gadisa, Pharmacy Department, College of Medicine and Health Sciences, Ambo University, Ambo, Ethiopia.
Email: direalexphar@ymail.com

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Background

According to GLOBOCAN, breast cancer is the most common cancer in women, accounting for 25.1% of all cancers and associated with higher incidence and mortality in developed countries.[1] Similarly, in Ethiopia, breast cancer is leading cancer among all-females and accounts for 24.4% with an estimated age-standardized mortality rate of 25 per 100,000 females.[2]

Despite the lifesaving or prolonging importance of chemotherapeutic agents used in breast cancer treatments, these agents have considerable and frequent side effects or toxicities.[3] Toxicities of breast cancer chemotherapy are higher during routine clinical care than clinical trials due to a higher prevalence of comorbidities, older age at the time of diagnosis, and poor performance status in clinical care.[4,5] This might be due to clinical trials that follow strict enrollment criteria and involve close monitoring of study participants.[6,7]

Similar standard chemotherapy dosage given to individuals may result in a wide variety of toxicities, which is an important problem in clinical practice.[8] Some of this variability is due to race or genetic factors of individuals.[9,10] Moreover, Ethiopian populations are genetically highly diverse than the rest of world populations in which unrecognized variation can lead to an increased risk of an adverse drug reaction (ADR).[11] On top of that, Africans, including Ethiopians, are underrepresented in cancer clinical trials.[12,13] Again, patient-reported toxicities help to appraise the breast cancer treatment experience than clinical trials.[7] Hence, the safety study of chemotherapy in a white race or developed country should be sought in a developing country like Ethiopia.

Previous reports in cancer patients in Ethiopia indicated that the prevalence of drug therapy problems was 74.7% in which 45.5% was attributed to ADR of chemotherapy.[14] The survey of cancer patient's preferred sources of information in Ethiopia found that 63.3% (350/556) of the patients on chemotherapy indicated the lack of information regarding the side effects of chemotherapy and their management.[15] Hence, identifying the most prevalent and serious toxicities and associated factors that increase the toxicity of chemotherapy will help health-care providers and patients to improve their understanding of ADRs which leads to better prevention and management of chemotherapy-related toxicities. Yet, data on the toxicity profile of breast cancer chemotherapy and associated factors from Africa are lacking.[16] Thus, the aim of the current study is to examine the toxicity profile of the two most commonly used regimens for breast cancers in Ethiopia: Doxorubicin-Cyclophosphamide (AC) and Doxorubicin-Cyclophosphamide→Cyclophosp (AC-T). Based on the literature review, this is the first study in Ethiopia to address this highly demanded and timely issue.

Patients and methods

This is a prospective cohort study of 146 women with breast cancer: 71 patients with breast cancer on AC regimen and 75 patients on AC-T regimen conducted at Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa from January 1 to September 30, 2017 GC. TASH is the only oncology center in Ethiopia. Women aged 18 years and above with proven breast cancer scheduled to receive neo/adjuvant or palliative chemotherapy with AC and AC-T regimens were included in the study and followed for a median of eight chemotherapy cycles or six months (range: three to six months). Forty-six (46) patients received four cycles of AC regimen, while 25 received six cycles of AC regimen, and 75 patients received eight cycles of AC-T regimen. Women receiving other regimens for breast cancer treatment were excluded.

Patients' demographics and pretreatment characteristics, medical records, laboratory investigations including complete blood counts, liver function test, and serum creatinine were collected. Biopsy reports describing tumor characteristics such as the site of the tumor, degree of differentiation, tumor size, and lymph node involvement were also recorded. In addition, Eastern Cooperative Oncology Group (ECOG) performance status,[17] weight, height, body mass index (BMI), chemotherapy panel (for chemotherapy groups as neo-adjuvant, adjuvant, or metastatic), and chemotherapy regimen were recorded.

The average proportion of chemotherapy dose-limiting toxicities such as leukopenia, anemia, neutropenia, peripheral neuropathy, and oral mucositis was considered as primary toxicity endpoints to determine

sample size with 80% power and 5% margin of error.[18] Accordingly, it needs at least 131 (i.e., 65 per each group) study participants. For the robustness of the study, we included more study participants than the minimum requirement per each group.

Women with breast cancer on the AC regimen took Doxorubicin (A) 60 mg/m^2 and Cyclophosphamide (C) 600 mg/m^2 as an intravenous infusion every 21 days for four or six cycles. And those on the AC-T regimen took Doxorubicin (A) 60 mg/m^2 and Cyclophosphamide (C) 600 mg/m^2 every 21 days for four cycles and followed by Paclitaxel (T) 175 mg/m^2 intravenous infusion every 21 days for four cycles. In addition, for every cycle of treatment, premedication with Ondansetron 8 mg, Dexamethasone 16 mg, Cimetidine 400 mg, and Metoclopramide 10 mg were given by intravenous infusion before the commencement of all chemotherapy regimens.

Ethical clearance

The study was approved by the institutional review board of the School of Pharmacy, College of Health Sciences, Addis Ababa University (Ref No: ERB/SOP/09/2016). Written informed consent was obtained from all patients prior to participation in the study.

Assessment for safety endpoint

Adverse events were graded using the national cancer institute common terminology criteria for adverse events, version 4.03.[19] Accordingly, grade 2 leucopenia (white blood cells count <3000–2000/mm^3), grade 2 anemia (hemoglobin level 8.0–10.0 g/dl), grade 2 thrombocytopenia (platelets count 75,000–50,000/mm^3), grade 2 neutropenia (absolute neutrophil count 1000–<1500/mm^3); grade 2 alanine/aspartate aminotransferase increment (3–5× normal upper limit, U/L), grade 2 creatinine increment (1.5–3× normal upper limit, mg/dL); alkaline phosphatase (ALP) increment (2.5–5× normal upper limit, U/L). Patients were personally interviewed for subjective toxicities such as nausea, vomiting, and their toxicity grades were assessed based on the diary maintained during their revisits. The laboratory values were recorded for all patients at the baseline (pretreatment) and every cycle of chemotherapy. The toxicity with the highest grade during any cycle was considered as the toxicity grade for that patient.

Statistical analysis

The Statistical Package for Social Sciences (Released 2013, IBM SPSS Statistics for Windows, Version 22.0; IBM Corp., Armonk, NY) software was used for the analysis. Descriptive parameters were expressed as percentages and frequencies, and continuous variables expressed as mean ± standard deviation (SD). Chi-square (χ^2) and t-test statistics were used to test the differences in toxicities between the two treatment arms. A backward binary logistic regression model was used to determine predictive factors for toxicity. Two-sided 0.05 significance level was used throughout the analysis.

Results

Socio-demographic and pretreatment clinical characteristics of participants

There were no statistically significant differences between the two regimens at enrollment in the mean age, BMI, presence of co-morbidity, histological classification of a tumor, ECOG performance and hematological laboratory values (Table 1). Pretreatment serum creatinine (0.92 and 0.9) and ALP (265.3 and 192) of patients were significantly higher for AC-T and AC regimens, respectively. The body surface area (BSA) at enrollment for patients on AC and AC-T regimen was significantly varied at 1.6 and 1.7 m^2, respectively (Table 1). The mean numbers of cycles for AC and AC-T regimen were 4.7 and 7.9, respectively. All patients with stage IV breast cancer received the AC regimen.

Toxicities of AC and AC-T regimen among the participants

Fatigue 144 (98.7%), dysgeusia 142 (97.3%), and skin hyperpigmentation 141 (96.6%) were the most frequent toxicities while nausea 136 (93.2%), vomiting 129 (88.4%), gastritis 122 (83.6%), and oral mucositis 106 (72.6%) were the most frequent gastrointestinal (GI) toxicities observed (Table 2). Peripheral neuropathy 108 (74.0%) and myalgia/arthralgia 110 (75.3%) were also among the frequent toxicities reported. Among the organ function test conducted, grade 1 and above ALP elevation 46 (31.5%), aspartate/alanine aminotransferase elevation 42 (28.8%), and creatinine elevation 32 (21.9%) were the common ones. Neutropenia 107 (73.3%), leukopenia 102 (69.9%), and anemia 51 (34.9%) were the frequent hematological toxicities recorded.

Arthralgia/myalgia (2.8% vs. 20.0%, P = 0.001), peripheral neuropathy (1.4% vs. 36.0%, P = 0.000), and gastritis (14.1% vs. 29.3%, P = 0.026) were among severe grade toxicities differences between AC and AC-T regimen, respectively. Anemia (16.9% vs. 2.7%, P = 0.004) and leukopenia (35.2% vs. 17.3%, P = 0.014) were also among the moderate and higher

Table 1. Socio-demographic, pretreatment clinical characteristics of patients with breast cancer on AC and AC-T regimens at TASH from January 1 to September 30, 2017 GC, N = 146.

	Regimen		
Baseline variables	AC (n = 71) (%)	AC-T (n = 75) (%)	P-value[a]
BSA (mean ± SD) (in m^2)	1.6 ± 0.2	1.7 ± 0.2	<0.05
BMI (mean ± SD) (in $kg{\cdot}m^{-2}$)	24.6 ± 14	25.8 ± 4.7	>0.05
Age (mean ± SD) (in years)	43.0 ± 12	41.8 ± 10.9	>0.05
Number of cycles (mean ± SD)	4.7 ± 0.9	7.9 ± 0.1	<0.05
Histological classification			>0.05
Ductal	63.0 (88.7)	68.0 (90.7)	
Lobular	1.0 (1.4)	5.0 (6.7)	
Metaplastic	1.0 (1.4)	0.0 (0.0)	
Mixed	2.0 (2.8)	1.0 (1.3)	
Mucinous	2.0 (2.8)	0.0 (0.0)	
Papillary	2.0 (2.8)	1.0 (1.3)	
Stage			
I	1.0 (1.4)	5.0 (6.7)	>0.05
II	14.0 (19.7)	34.0 (45.3)	0.000
III	28.0 (39.4)	36.0 (48.0)	>0.05
IV	28.0 (39.4)	0.0 (0.0)	0.000
Comorbidity			>0.05
Yes	9.0 (12.7)	13.0 (17.3)	
No	62.0 (87.3)	62.0 (82.7)	
ECOG performance			>0.05
0	2.0 (2.8)	1.0 (1.3)	
I	62.0 (87.3)	73.0 (97.3)	
II	4.0 (5.6)	1.0 (1.3)	
III	3.0 (4.2)	0.0 (0.0)	
Baseline laboratory results (mean ± SD)			
WBC ($10^3/mm^3$)	7.3 ± 2.9	7.3 ± 1.8	>0.05
ANC ($10^3/mm^3$)	4.2 ± 2.3	3.9 ± 1.6	>0.05
Hgb (g/dL)	13.7 ± 1.5	14 ± 1.2	>0.05
Lympho ($10^3/mm^3$)	2.3 ± 0.9	2.4 ± 0.7	>0.05
PLT ($10^3/mm^3$)	329.3 ± 137.2	299.7 ± 75.6	>0.05
SCr (mg/dL)	0.9 ± 0.2	0.92 ± 0.1	0.028
AST (U/L)	28.7 ± 18.2	26.8 ± 24.9	>0.05
ALT (U/L)	21.1 ± 15.5	25.7 ± 37.9	>0.05
ALP (U/L)	238.2 ± 186.8	192 ± 61.8	0.047

AC: Doxorubicin-Cyclophosphamide; AC→T: Doxorubicin-Cyclophosphamide→Paclitaxel; ALP: Alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; BMI: body mass index; BSA: body surface area; ECOG: Eastern Cooperative Oncology Group; Hgb: hemoglobin; Lympho: lymphocytes; PLT: platelet count; SCr: Serum creatinine; SD: standard deviation; TASH: Tikur Anbessa Specialized Hospital; WBC: white blood cell count.

[a]Association was determined by using chi-square and independent samples t-test statistics.

grade toxicities with statistically significant differences between AC and AC-T regimen.

Predictor factors for grade 2 and above primary toxicity endpoints

For grade 2 and above leukopenia, pretreatment white blood cell counts (adjusted odds ratio (AOR) = 0.452, P = 0.001) and stage IV breast cancer (AOR = 3.22, P = 0.015) were significant predictors. For anemia, older age (AOR = 1.08, P = 0.006), pretreatment hemoglobin (AOR = 0.43, P = 0.001), and BSA (AOR = 0.015, P = 0.024) were significant predictors. Old age (AOR = 1.04, P = 0.031) was a unique independent predictor for oral mucositis. Arthralgia (AOR = 11.18, P = 0.000) and myalgia (AOR = 5.21, P = 0.007) were significant predictors for moderate and higher grade peripheral neuropathy (see Table 3).

Discussion

Toxicities of chemotherapy are the major cause of dose discontinuation, dose delay, dose modification, or treatment extension which can lead to deterioration

Table 2. Non-hematological and hematological toxicity profile of AC and AC-T regimens among patients with breast cancer at TASH, from January 1 to September 30, 2017 GC, N = 146.

Regimen	AC (n = 71) (%)			AC-T (n = 75) (%)				Toxicity difference: AC vs AC-T regimen
	Grade			Grade				
Toxicity[a]	1	2	3	1	2	3	Overall (N) (%)	P-value
Constipation[b]	28 (39.4)	10 (14.1)	2 (2.8)	42 (56.0)	8 (10.7)	0 (0.0)	90 (61.6)	NS
Diarrhea[b]	28 (39.4)	5 (7.0)	6 (8.5)	36 (48.0)	10 (13.3)	3 (4.0)	88 (60.3)	NS
Gastritis[b]	8 (11.3)	38 (53.5)	10 (14.1)	4 (5.3)	40 (53.3)	22 (29.3)	122 (83.6)	0.026 (G3)
Oral mucositis[b]	8 (11.3)	32 (45.1)	8 (11.3)	9 (12.0)	39 (52.0)	10 (13.3)	106 (72.6)	NS
Nausea[b]	8 (11.3)	35 (49.3)	20 (28.2)	9 (12.0)	31 (41.3)	33 (44.0)	136 (93.2)	0.047 (G3)
Vomiting[b]	22 (31.0)	24 (33.8)	14 (19.7)	24 (32.0)	28 (37.3)	17 (22.7)	129 (88.4)	NS
Dysgeusia[b]	7 (9.9)	62 (87.3)	–	4 (5.3)	69 (92.0)	–	142 (97.3)	NS
SHP[b]	36 (50.7)	31 (43.7)	–	28 (37.3)	46 (61.3)	–	141 (96.6)	NS
Allergic reaction[b]	24 (33.8)	2 (2.8)	0 (0.0)	39 (52.0)	5 (6.7)	0 (0.0)	70 (47.9)	NS
Fatigue[b]	12 (16.9)	54 (76.1)	4 (5.6)	7 (9.3)	58 (77.3)	9 (12.0)	144 (98.6)	NS
Myalgia/arthralgia[b]	27 (38.0)	9 (12.7)	2 (2.8)	25 (33.3)	32 (42.7)	15 (20.0)	110 (75.4)	0.001 (G3)
PN[b]	34 (47.9)	4 (5.6)	1 (1.4)	28 (37.3)	14 (18.7)	27 (36.0)	108 (74.0)	0.000 (G3)
Infection[b,c]	0 (0.0)	6 (8.5)	0 (0.0)	0 (0.0)	7 (9.3)	0 (0.0)	14 (9.6)	NS
ΔSCr[b]	9 (12.7)	4 (5.6)	0 (0.0)	16 (21.3)	3 (4.0)	0 (0.0)	32 (21.9)	NS
ΔAST/ALT[b]	18 (25.4)	0 (0.0)	1 (1.4)	20 (26.7)	0 (0.0)	3 (4.0)	42 (28.8)	NS
ΔALP[b]	15 (21.1)	7 (9.9)	1 (1.4)	21 (28.0)	0 (0.0)	2 (2.7)	46 (31.5)	0.039 (G2/3)
Leukopenia[d]	31 (43.7)	21 (29.6)	4 (5.6)	33 (44.0)	11 (14.7)	2 (2.7)	102 (69.9)	0.014 (G2/3)
Anemia[d]	17 (23.9)	10 (14.1)	2 (2.8)	20 (26.7)	2 (2.7)	0 (0.0)	51 (34.9)	0.004 (G2/3)
Neutropenia[d,e]	5 (7.0)	16 (22.5)	23 (32.4)	4 (5.3)	24 (32.0)	19 (25.3)	107 (73.3)	NS
Lymphopenia[d]	31 (43.7)	10 (14.1)	5 (7.0)	25 (33.3)	11 (14.7)	1 (1.3)	83 (56.9)	NS

ALT: alanine amino transferase; ALP: alkaline phosphatase; AST: aspartate amino transferase; G2/3: grades 2 and 3; G3: grade 3; "–": no grade; NS: non-significant; PN: peripheral neuropathy; SCr: Serum Creatinine; SHP: skin hyperpigmentation; Δ: increment.

[a]All patients on both regimens developed grade 1 nail abnormalities (i.e, nail discoloration/onycholysis) and grade 2/complete alopecia.

[b]Non-hematological toxicity.

[c]One patient on the AC-T regimen had grade 4 infections (i.e., meningitis).

[d]Hematological toxicity.

[e]Ten (14.10%) and 6 (8.00%) of patients treated with AC and AC-T regimen were developed grade 4 neutropenia, respectively.

of quality of life of patients[5] which is congruent to our findings. Consequently, identifying the toxicities profile and related factors of widely used AC and AC-T regimens in our population have paramount importance in clinical practice.

The treatment of breast cancer by AC or adding taxane into the AC regimen significantly increased disease-free survival (DFS) and overall survival (OS).[20] However, all anticancer drugs are toxic for the tumor as well as the host.[21]

All patients on both regimens suffered from mild grade nail abnormalities (i.e., nail discoloration and/or onycholysis) and complete alopecia. Chemotherapy-induced alopecia has no fully effective preventive methods that further compromise the patient's quality of life.[22] In addition, 141 (96.6%) of study participants developed grade ½ skin hyperpigmentation. The nail abnormalities might be due to extensive denervation by paclitaxel (i.e., antimitotic activity) of continuously dividing nail matrix cells. And similar neurogenic mechanisms have been postulated for anthracycline-induced nail abnormalities.[23]

The study conducted by Peoples et al. and others showed a high prevalence (58%–94%) of chemotherapy-related fatigue in particular during the beginning of chemotherapy with doxorubicin containing regimens.[24] Likewise, overall grade fatigue was the most prevalent 144 (98.7%), including 13 (8.9%) grade 3 toxicity reported in our study with high frequency during the first cycle, 136 (93.2%), and it remains slightly stable in intensity while taking the drugs and decline after the end of chemotherapy.[24,25] A reason for slight stability could be habituation (i.e., a shift in internal norm) or response shift to experience fatigue.[26] Even though it is not statistically significant, more patients on AC-T regimen in the present study suffered from severe fatigue than those on the AC regimen (12% vs. 4.5%).

GI toxicities were the most distressing early toxicity and common complication of cytotoxic cancer

Table 3. Predictor factors for grade 2 and above primary toxicity endpoints by logistic regression, from January 1 to September 30, 2017 GC, N = 146.

			Exp (B) (AOR)[a]	95% CI for Exp (B)	
				Lower	Upper
Independent predictors for leukopenia ≥2 grade					
Factors	Pretreatment WBC	P-value = 0.001	0.452	0.281	0.728
	Stage IV versus others	P-value = 0.015	3.22	1.223	8.486
Independent predictors for anemia ≥2 grade					
Factors	Age	P-value = 0.006	1.08	1.022	1.144
	Pretreatment hemoglobin	P-value = 0.001	0.43	0.262	0.691
	BSA	P-value = 0.024	0.015	0.000	0.580
Independent predictors for peripheral neuropathy ≥2 grade					
Factors	Grade≥2 Arthralgia	P-value = 0.000	11.18	3.264	38.305
	Grade≥2 myalgia	P-value = 0.007	5.21	1.561	17.401
Independent predictors for oral mucositis ≥2 grade					
Factors	Age	P-value = 0.031	1.04	1.003	1.068
Independent predictors for fatigue[b] ≥2 grade					
Factors	Grade 2 Skin hyperpigmentation	P-value = 0.012	4.51	1.383	14.681
Independent predictors for dysgeusia[b] grade 2					
Factors	Grade ≥ stomatitis	P-value = 0.011	5.50	1.489	20.337
	Grade ≥ nausea	P-value = 0.028	5.46	1.196	24.912

AOR: adjusted odds ratio; BSA: body surface area; WBC: white blood cell count; CI: confidence interval.

[a]All socio-demographic and clinico-pathological data in Table 1 and toxicities in Table 2 were analyzed using logistic regression model one by one, and those showed P ≤ 0.05 in logistic regression model were finally included in a backward multivariable logistic regression model. Hence, only significant predictors in the final backward multivariable logistic regression model were presented in Table 3 above. Accordingly, unlike other primary toxicity endpoints, no significant predicting factors identified for neutropenia ≥ grade 2.

[b]They are not primary toxicity endpoints rather the most frequently reported by the study participants.

Note: Grade 0/1 toxicity was used as a reference category for categorical predictors and outcome variables whereas age, BSA and pretreatment WBC were used as continuous predictor variables.

chemotherapy.[27] Hence, the majority of our study participants experienced moderate severity GI toxicities during the second and third cycles of chemotherapy. Patients on the AC-T regimen experienced significant severe nausea (P = 0.047) and gastritis (P = 0.026) than those on the AC regimen. Those adverse events were mainly encountered during the AC component of the AC-T regimen and increasing BSA (AOR = 5.98, 95% CI: 0.75–47.72, P = 0.092) was also the major risk factor for severe gastritis (data not shown).

Our study showed a gap in controlling nausea and vomiting with antiemetic prophylaxis. More than 88% of our study participants reported nausea and vomiting during the course of treatment; including 36.3% and 21.2% grade 3 nausea and vomiting, respectively, though all of them received ondansetron-based antiemetic agents. Our finding is similar to the study done in the Republic of Korea.[28] Hence, the increased frequency of nausea and vomiting warrant consideration of adding an antiemetic neurokinin-1–receptor antagonists such as aprepitant, which is more effective than 5-HT3 antagonist ondansetron, to reduce these GI side effects[29] in addition to solving sleep problems, anxiety, and history of nausea and vomiting.[28]

The fact that our study showed a higher rate of severe oral mucositis (12.3% vs. 2.8%) in the regimen compared to Barasch and Epstein's meta-analysis results of 515 patients with breast cancer.[30] The higher rate of oral mucositis in our patients might be related to patients' lack of adequate information regarding oral self-care in managing oral mucositis[31] and the absence of oral assessment prior to initiation of cytotoxic therapy to treat oral/dental infection.[30]

Chemotherapy is also known for its different grade hepatic and renal toxicities.[25] There was a statistically significant elevation of ALP among those received AC than AC-T regimen (11.3% vs. 2.7%, P = 0.039) which was due to the significant mean difference in pretreatment ALP level between the two regimens (238.2 vs. 192, P = 0.047). This might be due to metastatic disease like liver failure and bone fractures,[32] as all of our stage IV patients, having higher baseline ALP than other stages (277.8 vs. 197.8, P = 0.028), received AC regimen.

The rate of neurotoxicity in our study, 108 (74.0%), is similar to other studies[33,34] warranting a need to detect and manage it as early as possible. Moreover, a significantly higher rate of severe arthralgia/myalgia

(20.0% and 2.8%, P = 0.001) and peripheral neuropathy (36.0% and 1.4%, P = 0.000) were observed among patients on AC-T regimen than on AC regimen. This difference could be from the inherent toxicities characteristics of the paclitaxel component of AC-T regimen.[5,35,36] This neurotoxicity has appeared early during treatment[37] which is congruent to our study. However, the clinical trial by Hershman et al.[33] showed that sensory neuropathy (i.e., numbness, tingling, and paresthesia) was difficult to manage.

The incidence of severe peripheral neuropathy in our patients was relatively higher (4 vs. 27) than reported in other randomized controlled trials.[38,39] During the treatment with AC regimen and AC part of the AC-T regimen, our study participants reported only mild peripheral neuropathy compared to randomized controlled trials.[40] Hence, the cumulative dose of AC chemotherapy might increase the risks of paclitaxel-induced severe peripheral neuropathy later.[41,42] The study by de Graan et al. in Caucasians indicated that female CYP3A4*22 carriers had an increased risk of developing severe neurotoxicity during paclitaxel therapy.[43] These observations may guide future studies regarding pharmacogenomics of paclitaxel in Ethiopian breast cancer patients.

In addition to non-hematological toxicities reported above, the incidences of hematological toxicities in our study participants were higher than some reported studies[44,45] and lower than other studies.[4,9] The difference could be the result of variability in the pharmacogenomics of those population as those drugs are substrates for cytochrome (CY)P450 3A4, CYP450 3A5, CYP450 2B6, CYP450 2C8, CYP450 2C9, and CYP450 2C19; and drug transporters such as adenosine triphosphate-binding cassette sub-family B member 1 (ABCB1) and solute carrier family 22 (SLC22A1),[46–49] and excision repair cross-complementing 1 (ERCC1)[10] which are highly polymorphic. Unfortunately, in addition to having low pretreatment blood counts (AOR = 0.430–0.452, P = 0.001), older age (AOR = 1.08, P = 0.006), having stage IV breast tumor (AOR = 3.22, P = 0.015) and lower BSA (AOR = 0.015, P = 0.024) in our study, Ahmed et al. identified Ethiopian patients with breast cancer carrying CYP2J2*7 allele are at a higher risk for chemotherapy-induced hematologic toxicities.[16] Hence, they may require prior support and close follow-up during chemotherapy.[8,50–52]

Older age (AOR = 1.04, P = 0.031) is the independent predictor for grades 2–3 oral mucositis in the present study. The multivariate logistic regression model showed only grade 2 skin hyperpigmentation (AOR = 4.51, P = 0.012) became a unique predictor for moderate and higher grade fatigue in our patients even though the other study reported younger age.[24]

Limitation of the study

We did not report the efficacy of both regimens, in terms of DFS and OS, and late toxicities that could happen long after the completion of chemotherapy courses. In addition, because of financial problems, we could not conduct the pharmacogenomics study that might contribute to the high incidences of toxicities in our study participants. The response of the treating clinicians to the reported side effects is also unknown due to patients' reported outcome nature of the study. It is also possible that the retrospective self-reporting of side effects at three weeks' intervals perhaps introduced recall bias for participants' responses regarding the subjective toxicities.

Conclusion

In general, a very high rate of both hematological and non-hematological adverse events is noted among patients with breast cancer on AC and AC-T regimens chemotherapy in Ethiopia. However, patients who received AC regimen suffered more from hematological abnormalities and ALP increment, while those on AC-T regimen experienced more severe arthralgia/myalgia, peripheral neuropathy, and gastritis. Improving pretreatment hematological and other laboratory values will be important in reducing the incidences of hematological and other toxicities. Moreover, further long-term follow-up study including genetic profiling of patients would help greatly in identifying and managing those toxicities optimally.

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Author Contributions

DAG conceived the research idea, collected the data, and performed data analysis and interpretation. DAG also wrote the original draft of the manuscript. DAG and GY critically reviewed and edited the manuscript from the first draft to the final version. All authors critically reviewed the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Human Research Ethics Committee or Institutional Review

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ORCID iD

Diriba Alemayehu Gadisa https://orcid.org/0000-0001-7047-2394

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