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Racial differences in acute toxicities of neoadjuvant or adjuvant chemotherapy in patients with early-stage breast cancer

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ABSTRACT

Background: Racial disparities in breast cancer outcomes are attributed to differences in baseline tumour characteristics and biology, stage, age, ethnic background and socioeconomic factors. However, little is known about racial differences in treatment-related toxicities. We hypothesised that racial/ethnic differences result in differential tolerance to chemotherapy potentially, leading to compromised dose intensity/density of chemotherapy in patients with early-stage breast cancer.

Methods: Data were collected from patients treated at five international centers for early breast cancer with the same adjuvant/neoadjuvant chemotherapy (FEC 100: fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2,every 21 d for 3–6 cycles). Toxicities were assessed by first episode of $\geqslant$grade 2 toxicity.

Results: Toxicities were compared according to four race/ethnicity groups (103 Caucasian, 30 African American, 164 Asian, and 34 Hispanic patients). Tumour characteristics across four race/ethnicity groups were similar. Asians had a significantly higher rate of grade 3 haematologic toxicity than Caucasians, African Americans or Hispanic women (32%, 16%, 10%, and 15%, respectively; $p < 0.05$). In multivariate analysis, only lower BMI was associated with a higher incidence of $\geqslant$grade 3 toxicities. However, no significant differences in chemotherapy dose intensity/density were shown across the four race/ethnicity groups.

Conclusion: Racial differences in acute toxicity were noted in women with breast cancer who were treated with FEC 100 chemotherapy, suggesting that extrapolating toxicities from chemotherapy across ethnicities is not possible and emphasising the need to validate safety of chemotherapeutic regimens in patients of different ethnicities by enhancing the participation of minorities in clinical trials.

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1. Introduction

The existence of racial disparities in cancer survival has been established, and the possible reasons have been dissected and widely debated. Retrospective and population-based epidemiologic studies have indicated reduced survival rates among African American women with breast cancer compared with their Caucasian counterparts.[1,2] The Henry Ford Health System reported that 10-year overall mortality from breast cancer was higher in African American women than in Caucasian patients (25% versus 18%, respectively; $p = 0.03$).[3] The Surveillance, Epidemiology and End Results (SEER) database also recognised the higher mortality rates seen in African Americans and other minorities compared with non-Hispanic white breast cancer patients. Alternative studies conducted in Hawaii investigated the survival rates of Japanese and Chinese women versus non-Hispanic whites and found higher survival rates in the Asian cohort; however, the Asian patients presented with less advanced stage of disease.[4,5]

Chemotherapy is the standard treatment for many different forms of cancer; therapy for nonmetastatic breast cancer often involves the use of combined chemotherapeutic agents using anthracycline-based regimes. Recent studies indicate that dose dense chemotherapy is a more effective strategy than conventional schedules.[6] The combination of cytotoxic agents and dose dense schedule has proven to be superior in breast cancer treatment; however, it has concurrently compromised patient quality of life as a result of toxicity. The most common adverse events associated with adjuvant chemotherapy include myelosuppression, febrile neutropenia, alopecia, and gastrointestinal toxicities. If persistent, these toxicities can lead to delays or reductions, which can ultimately compromise long-term outcomes.[7–9]

A question that has been rarely addressed by previous studies includes racial difference in tolerance to chemotherapy, which may also result in racial disparities in outcomes. Data are limited regarding the racial differences among multiple races in cancer treatment-related toxicities. A retrospective study reported the higher acute toxicity experienced in Asian patients versus their Caucasian counterparts receiving adjuvant doxorubicin based chemotherapy.[10] Neutropenia occurred significantly higher in Asian women (52% grade 3 and 25% grade 4 neutropenia for Asians versus 3.4% grade 3 neutropenia and 0.3% grade 4 neutropenia for Caucasians). According to the study by Toi et al. involving Japanese women, the incidence of neutropenic fever was noted to be higher than expected on the FEC 100 regimen, compared to the results published by the French adjuvant study group, which included mainly Caucasians (8.4% versus 20%).[11,12]

The potential causes for inter-ethnic variabilities in toxicities from chemotherapeutic agents remain unclear. Variability could be a direct result of inherent differences in associated co-morbidities, socio-demographic factors leading to poor compliance (especially with supportive care therapy), pharmacokinetics, pharmacogenomics and incorrect association with BMI and BSA calculations.[2,13,14] It is important to recognise the distinct chemotherapy-related toxicity profiles of individual ethnic groups, in order to improve outcomes for minority women and to decrease the health disparity gap. In an effort to bridge the aforementioned gap in breast cancer care, we collaborated with investigators at the University of Calgary, Hong Kong, and the Tokyo Metropolitan Komagome Hospital to explore the ethnic differences in early breast cancer outcome and toxicity. We conducted a retrospective study of early breast cancer patients who received the standard FEC 100 regimen (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2). Our data focus on toxicity results across four races/ethnicities (Caucasian, African American, Asian, Hispanic), and our aim was to highlight chemotherapy tolerance variation for patients on a standard treatment. We hypothesised that racial/ethnic differences result in differential tolerance to chemotherapy, potentially leading to compromised dose intensity or density of adjuvant or neoadjuvant chemotherapy in patients with early-stage breast cancer and affecting patient outcomes.

2. Patient and method

2.1. Patient selection

Data were collected from five international collaborating centers (University of Miami, H. Lee Moffitt Cancer Center, JBCRG (Japan Breast Cancer Research Group), University of Hong Kong, and Tom Baker Cancer Center) at which patients have been treated for early breast cancer with the FEC 100 containing adjuvant or neoadjuvant chemotherapy (FEC 100: fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2, intravenously every 3 weeks, for 4–6 cycles) between 1999 and 2007.

Asian women from Japan and Hong Kong received neoadjuvant chemotherapy with four cycles of FEC 100 followed by four cycles of docetaxel. All other women from the United States and Canada were treated with FEC 100 containing regimens as part of standard of care. Haematopoietic growth factors were not prophylactically used in all centers. This study was approved by the Institutional Review Board at each institution.

2.2. Data collection

Clinical charts and treatment records were reviewed at each center using a standard data collection sheets provided by the University of Miami. The data included patient demographics, self-assigned race/ethnicity, height, weight, comorbidities, baseline tumour characteristics, treatment course, dates of treatment, the use of haematopoietic growth factors and antiemetic premedications, the number of cycles of FEC100 delivered, baseline white blood cell and absolute neutrophil counts (ANC), first episode of grade 2 or higher toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 by the National Cancer Institute, and outcomes related to acute toxicity. Occurrences of single or multiple episodes of toxicity were collected if they were simultaneous.

Haematologic toxicities included neutropenic fever and cytopenias leading to treatment changes. For cytopenias including neutropenia, anaemia and thrombocytopaenia

were counted only if they led to serious outcomes (that is, dose reduction, dose delay, discontinuation of therapy or hospitalisation) to avoid the measurement bias. For example, women who were treated as part of clinical trials were likely to have more frequent laboratory tests, including blood counts, than women who got therapy as part of standard of care. In addition, because toxicity that did not impact dose intensity is unlikely to result in a deleterious effect on outcome, it was not included.

The following non-haematologic toxicities were included in this analysis: nausea, vomiting, diarrhoea, mucositis, hepatotoxicity, hand-food syndrome, and infection, not related to neutropenia.

2.3. Statistical analysis

Descriptive analyses of the patient characteristics and the toxicities were performed for all patients and for the four racial/ethnic groups (Caucasian, African American, Hispanic and Asian).

Chi-square test, Fisher's exact test and ANOVA were used to compare race/ethnicity groups. Missing values were excluded for percentage and mean. If overall test for difference was significant ($p \leqslant 0.05$), then pairwise comparison with Bonferroni adjustment were conducted. Univariate and multivariate logistic regression analyses were used to evaluate effect of potential predictors of grade 3 or higher toxicity versus grade 2 or no toxicity, and of haematologic grade 3 or higher toxicity as compared to any grade 2 or no toxicity. Statistical analyses were conducted using SAS software version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patient and tumour characteristics

This study included Caucasian ($n = 103$, 20 from the United States and 83 from Canada), African American ($n = 30$, 29 from the United States and one from Canada), Asian ($n = 164$, 141 from Japan and 23 from Hong Kong) and Hispanic ($n = 34$, 32 from the United States and two from Canada) patients.

Baseline patient characteristics were similar across the four racial groups except body mass index (BMI) and comorbidities (Table 1). Approximately 70% of patients were younger than 55 years, and 54% were premenopausal at the time of diagnosis. African American and Hispanic patients were more likely to be obese or overweight and Asians had the lowest BMI, with a mean of 23 compared to 28, 30 and 29 for Caucasian, African American and Hispanic patients, respectively. Similarly, African American and Hispanic women were more likely than Caucasian or Asian women to have comorbidities, most commonly hypertension and diabetes.

The majority of patients in all ethnic groups were treated for stage II breast cancer. Ninety three percent of Caucasians had axillary lymph node involvement compared to 67% of African Americans, 87% of Hispanics and 79% of Asians. Asian women had less high grade of tumour than the other racial groups and African-American women were more likely to have hormone receptor negative tumours than the other racial groups. Detailed information is provided in Table 2.

3.2. Toxicity

The complete toxicity analysis for each ethnic cohort is presented in Table 3. Most occurrences of first toxicity were recorded on first cycle across different race/ethnic groups (72% in Caucasians, 69% in African Americans, 52% in Hispanics, and 82% in Asians), which is shown in Fig. 1.

3.2.1. Grade 2 or higher toxicity as a first episode

Overall, 181 (54.7%) patients had grade 2 or higher toxicity as first episode, and the corresponding rate was statistically significantly higher among Caucasians (72.8%) than in African Americans (33.3%) and Asians (47%), mostly due to higher incidence of grade 2 non-haematologic toxicity in Caucasians. The incidence of overall toxicity is shown in Fig. 2. Twenty-six percent of patients had haematologic toxicity, 33% had non-haematologic toxicity, and 4% had both haematologic and non-haematologic toxicities simultaneously. No significant toxicity difference among different race/ethnicity groups was observed for grade 2 or higher haematologic toxicity; however, there was a significantly higher grade 2 or greater non-haematologic toxicity for Caucasians (55%) than for African Americans (23%) and Asians (20%). The majority of non-haematologic toxicity were nausea and vomiting. However, premedications to prevent chemotherapy-induced nausea/vomiting were different for patients at the Canadian site, which routinely did not use 5-HT3 antagonist unlike other centers. Of the 103 total Caucasian patients in our study, 83 were treated in Canada and only 45 out of 83 (54%) patients did receive 5-HT3 antagonist. This could partly explain a significantly higher non-haematologic toxicity in Caucasians

3.2.2. Grade 3 or higher toxicity as a first episode

About one-third of patients (31%) had grade 3 or higher toxicity, and there were no race/ethnicity differences ($p = 0.810$). However, the rate of haematologic grade 3 or higher toxicity was significantly higher in Asian women (32.3%) than in Caucasians (15.5%) and African Americans (10%), whereas the rate of non-haematologic grade $\geqslant 3$ toxicity was very low in Asians (1.8%) compared with that shown in Caucasians (14.6%) and African Americans (16.7%) (Fig. 3). Grade 4 adverse events in Asians were also higher (13.4%) compared with Caucasian (3.9%) and African American (5.9%).

3.2.3. Outcomes from toxicity

We have reviewed the outcomes including dose reduction, dose delay, therapy discontinuation, or required hospitalisation due to toxicities across the different race/ethnicity; we found no significant differences between the groups (23% for Caucasians, 13% for African Americans, 38% for Hispanics and 27% for Asians). Asian and Hispanic women required more frequent hospitalisation, and Asian women had the highest (3%) discontinuation of therapy due to toxicity.

3.2.4. Predictors of grade 3 or higher toxicity

In univariate analysis including race, age, comorbidity and BMI, the significant predictor for lesser grade 3 or higher toxicity was high BMI $\geqslant$ 30 (OR 0.47, $p = 0.045$) and BMI 25 to <30 (OR 0.57, $p = 0.072$). It remained to be predictive for less toxicity in multivariate analysis (Table 5).

Table 1 – Patient characteristics by race/ethnicity.

Variable	All		White		Black		Hispanic		Asian		P[b]
	N	%	N	%	N	%	N	%	N	%	
Total patients[a]	331	100.0	103	100.0	30	100.0	34	100.0	164	100.0	
Age at diagnosis											
<55	232	70.1	76	73.8	21	70.0	20	58.8	115	70.1	0.730
⩾55	99	29.9	27	26.2	9	30.0	14	41.2	49	29.9	
Mean (Std)	48.9 (9.7)		48.4 (9.8)		49.9 (10.2)		49.4 (10.9)		48.9 (9.4)		0.720
Median (Range)	49 (21–74)		50 (27–47)		52 (24–68)		48 (21–68)		49 (31–69)		
Menopausal status											
Pre-menopausal	177	54.3	53	52.0	16	53.3	18	52.9	90	56.3	0.917
Post-menopausal	149	45.7	49	48.0	14	46.7	16	47.1	70	43.8	
Missing	5	1.5	1	1.0	–	–	–	–	4	2.4	
Body Mass Index (BMI)[c]											
<25	190	58.5	50	48.5	6	20.0	11	32.4	123	77.8	<.0001
25 to <30	78	24.0	27	26.2	13	43.3	8	23.5	30	19.0	
⩾30	57	17.5	26	25.2	11	36.7	15	44.1	5	3.2	
Missing	6	1.8	–	–	–	–	–	–	6	3.7	
N	325		103		30		34		158		<.0001
Mean (SD)	25.6 (6.3)		27.6 (7.7)[c]		29.9 (6.6)[e]		29.3 (5.6)[f]		22.7 (3.5)[c,e,f]		
Median (Range)	24.0 (16.2–56.6)		25.3 (17.8–6.6)		29.1 (18.4–48.2)		28.6 (19.7–39.8)		22.1 (16.2–35.8)		
ECOG performance status											
0	312	94.3	84	81.6	30	100.0	34	100.0	164	100.0	<.0001
1	19	5.7	19	18.4	–	–	–	–	–	–	
Comorbidity											
Yes	78	25.1	26	25.2	13	56.5	10	47.6	29	17.7	<.0001
No	233	74.9	77	74.8	10	43.5	11	52.4	135	82.3	
Missing	20	6.0	–	–	7	23.3	13	38.2	–	–	
HTN/DM	53	17.2	14	13.6	11	52.4	8	38.1	20	12.2	<.0001
Other comorbidity/No	256	82.8	89	86.4	10	47.6	13	61.9	144	87.8	
Missing	22	6.6	–	–	9	30.0	13	38.2	–	–	
Number of comorbidity (N = 78)											
1	65	83.3	19	73.1	11	84.6	9	90.0	26	89.7	
2	11	14.1	6	23.1	2	15.4	1	10.0	2	6.9	
3	2	2.6	1	2.8	–	–	–	–	1	2.5	
Type of comorbidity[d]											
Hypertension (HTN)	45	13.6	10	9.7	10	33.3	7	20.6	18	11.0	
Diabetes (DM)	11	3.3	4	3.9	2	6.7	1	2.9	4	2.4	
Respiratory system	11	3.3	8	7.8	2	6.7	–	–	1	0.6	
Cardiac	9	2.7	2	1.9	1	3.3	3	8.8	3	1.8	
Genitourinary	9	2.7	5	4.9	–	–	–	–	4	2.4	
Gastrointestinal	7	2.1	5	4.9	–	–	–	–	2	1.2	
Hepatitis	1	0.3	–	–	–	–	–	–	1	0.6	

[a] 103 White (20 from United States, 83 from Canada), 30 Black (29 from United States, 1 from Canada), 34 Hispanic (32 from United States, 2 from Canada) and 164 Asian (141 from Japan, 23 from Hong Kong).

[b] Chi-square test, Fisher's exact test or ANOVA. Missing values are excluded for the test and percentage. If overall test was significant ($p \leqslant 0.05$), then pairwise comparison with Bonferroni adjustment were conducted; significant difference are denoted as follows: [a]Black versus White, [b]Hispanic versus White, [c]Asian versus White, [d]Hispanic versus Black, [e]Asian versus Black and [f]Asian versus Hispanic.

[c] BMI range (kg/m^2): <25 = underweight (<18.5) or normal weight (18.5 to <25), 25 to <30 = overweight, ⩾30 = obese.

[d] Patients are counted in multiple categories depending on the number of comorbidities.

Table 2 – Disease and treatment characteristics: total patients and by race/ethnicity.[a]

Variable	All		White		Black		Hispanic		Asian		P[b]
	N	%	N	%	N	%	N	%	N	%	
Total patients[a]	331	100.0	103	100.0	30	100.0	34	100.0	164	100.0	
T-stage											
T0–T1	80	24.2	39	37.9[c]	9	30.0[e]	13	39.4[f]	19	11.6[c,e,f]	<.0001
T2–T4	250	75.8	64	62.1	21	70.0	20	60.6	145	88.4	
Axillary lymph node disease (n = 224)											
Yes	270	83.3	96	93.2[a,c]	20	66.7[a]	27	87.1	127	79.4[c]	0.001
No	54	16.7	7	6.8	10	33.3	4	12.9	33	20.6	
Disease stage											
I or II	271	82.4	77	75.5	23	76.7	27	81.8	144	87.8	0.062
III	58	17.6	25	24.5	7	23.3	6	18.2	20	12.2	
Histology grade (n = 251)											
High	120	47.8	55	53.4[c]	18	64.3[e]	13	43.3[f]	34	37.8[c,f]	<.0001
Moderate	91	36.3	43	41.7	9	32.1	15	50.0	24	26.7	
Low	40	15.9	5	4.9	1	3.6	2	6.7	32	35.6	
Oestrogen receptor (n = 329)											
Positive	230	69.9	75	73.5[a]	11	36.7[a,d,e]	28	82.4[d]	116	71.3[e]	<.001
Negative	99	30.1	27	26.5	19	63.3	6	17.6	47	28.8	
Progesterone receptor (n = 329)											
Positive	192	58.4	73	71.6[a,c]	9	30.0[a,d]	24	70.6[d]	86	52.8[c]	<.0001
Negative	137	41.6	29	28.4	21	70.0	10	29.4	77	47.2	
HER2[c] (n = 309)											
Positive	73	23.6	23	27.1	7	24.1	11	33.3	32	19.8	0.304
Negative	236	76.4	62	72.9	22	75.9	22	66.7	130	80.2	
Mastectomy											
Yes	211	63.7	80	77.7	19	63.3	23	67.6	89	54.3	0.002
No	120	36.3	23	22.3	11	36.7	11	32.4	75	45.7	
Sentinel lymph node											
Positive	64	19.3	11	10.7	6	20.0	11	32.4	36	22.0	
Negative	62	18.7	15	14.6	12	40.0	13	38.2	22	13.4	
Not done/missing (n = 2)	205	62.0	77	74.8	12	40.0	10	29.4	106	64.6	
Number of LN sampled[d] (n = 315)											
0	5	1.6	1	1.0	1	4.0	–	–	3	1.9	
1–3	25	7.9	4	3.9	–	–	2	7.1	19	11.9	
4 or more	285	90.5	97	95.1	24	96.0	26	92.9	138	86.2	
Number of LN positive among patients with 1 or more LN removed[d]											
0	107	34.5	9	8.9	6	25.0	9	32.1	83	52.9	<.0001
1–3	123	39.7	45	44.6	14	58.3	11	39.3	53	33.8	
4 or more	80	25.8	47	46.5	4	16.7	8	28.6	21	13.4	
Chemotherapy											
Neoadjuvant	174	52.6	1	1.0	5	16.7	4	11.8	164	100.0	<.0001
Adjuvant	157	47.4	102	99.0	25	83.3	30	88.2	–	–	
G_CSF[c]											
Yes	124	38.0	7	6.9[c]	6	20.7[e]	4	11.8[f]	107	66.1[c,e,f]	<.0001
No	202	62.0	94	93.1	23	79.3	30	88.2	55	34.0	
Radiation (n = 323)											
Yes	241	74.6	77	75.5	18	60.0	20	58.8	126	80.3	0.015
No	82	25.4	25	24.5	12	40.0	14	41.2	31	19.7	

[a] 103 White (20 from United States, 83 from Canada), 30 Black (29 from United States, 1 from Canada), 34 Hispanic (32 from United States, 2 from Canada) and 164 Asian (141 from Japan, 23 from Hong Kong).

[b] Chi-square test, Fisher's exact test, or ANOVA. Missing values are excluded for the test and percentage. If overall test was significant ($p \leqslant 0.05$), then pairwise comparison with Bonferroni adjustment was conducted; significant differences are denoted as follows: [a]Black versus White, [b]Hispanic versus White, [c]Asian versus White, [d]Hispanic versus Black, [e]Asian versus Black and [f]Asian versus Hispanic.

[c] Human epidermal growth factor receptor 2.

[d] P value for comparison 0 versus 1 or more.

We have evaluated the potential predictors of haematologic grade 3 or higher toxicity using logistic regression analysis. Asian race and low BMI (underweight or normal weight, BMI <25) were associated with haematologic grade 3 or higher toxicity (Table 5). After controlling for potential confounding variables, the likelihood of haematologic grade 3 or higher toxicity was about 1.8 times higher in Asian than in Caucasian patients ($p = 0.085$), and patients with higher BMI were associated with less haematologic grade 3 or higher toxicity (Table 5). Normal or underweight women with BMI <25 were 2.6 times more likely to develop grade 3 or higher haematologic toxicity than obese women with BMI $\geqslant 30$ ($p = 0.086$).

Table 3 – Toxicity (first episode) by race/ethnicity (patient level).

	All		White		Black		Hispanic		Asian		P[a]
	N	%	N	%	N	%	N	%	N	%	
Total patients	331	100.0	103	100.0	30	100.0	34	100.0	164	100.0	
Worst grade											
1: Mild or no toxicity	150	45.3	28	27.2	20	66.7	15	44.1	87	53.0	
2: Moderate	78	23.6	45	43.7	2	6.7	9	26.5	22	13.4	
3: Severe	76	23.0	26	25.2	8	26.7	10	29.4	33	20.1	
4: Life-threatening/disabling	26	7.9	4	3.9	–	–	–	–	22	13.4	
Grade 2 or higher	181	54.7	75	72.8[a,c]	10	33.3[a]	19	55.9	77	47.0[c]	<.0001
Number of simultaneous episodes/Type											
Only 1	123	37.2	46	44.7	7	23.3	15	44.1	55	33.5	
Haematologic	60	18.1	16	15.5	2	6.7	6	17.6	36	22.0	
Non-haematologic	63	19.0	30	29.1	5	16.7	9	26.5	19	11.6	
Multiple	58	17.5	29	28.1	3	10.0	4	11.8	22	13.4	
2	49	14.8	26	25.2	3	10.0	4	11.8	16	9.8	
3	6	1.8	–	–	–	–	–	–	6	3.7	
4	3	0.9	3	2.9	–	–	–	–	–	–	
Haematologic	11	3.3	2	1.9	1	3.3	1	2.9	7	4.3	
Non-haematologic	33	10.0	25	24.3	2	6.7	1	2.9	5	3.0	
Both	14	4.2	2	1.9	–	–	2	5.9	10	6.1	
Haematologic[b]	85	25.7	20	19.4	3	10.0	9	26.5	53	32.3	0.021
Non-haematologic[b]	110	33.2	57	55.3[a,c]	7	23.3[a]	12	35.3	34	20.7[c]	<.0001
Grade 3 or higher	103	31.1	30	29.1	8	26.7	10	29.4	55	33.5	0.810
Number of simultaneous episodes/Type											
Only 1	88	26.6	24	23.3	8	26.7	10	29.4	46	28.0	
Haematologic	65	19.6	13	12.6	3	10.0	5	14.7	44	26.8	
Non-haematologic	23	6.9	11	10.7	5	16.7	5	14.7	2	1.2	
Multiple	15	4.5	6	5.8	–	–	–	–	9	5.5	
2	14	4.2	6	5.8	–	–	–	–	8	4.9	
3	1	0.3	–	–	–	–	–	–	1	0.6	
Haematologic	10	3.0	2	1.9	–	–	–	–	8	4.9	
Non-haematologic	3	0.9	3	2.9	–	–	–	–	–	–	
Both	2	0.6	1	1.0	–	–	–	–	1	0.6	
Haematologic[c]	77	23.3	16	15.5[c]	3	10.0[e]	5	14.7	53	32.3[c,e]	0.002
Non-haematologic[c]	28	8.5	15	14.6[c]	5	16.7[e]	5	14.7	3	1.8[c,e]	0.003

[a] Chi-square test. If test was significant ($p \leqslant 0.05$), then pairwise comparison with Bonferroni adjustment ($p \leqslant 0.008$) were conducted. Significant differences are denoted as follows: [a]Black versus White, [b]Hispanic versus White, [c]Asian versus White, [d]Hispanic versus Black, [e]Asian versus Black and [f]Asian versus Hispanic.

[b] Includes 14 patients, who had simultaneous haematologic and non-haematologic grade 2 or higher toxicity and are therefore counted in both categories.

[c] Includes two patients who had simultaneous haematologic and non-haematologic grade 3 or higher toxicity.

4. Discussion

This multicenter study is the first to examine toxicity variation between ethnic groups receiving the same chemotherapy treatment for breast cancer. Our results indicate that there are important differences in the acute toxicities experienced by Caucasian, African American, Hispanic and Asian women receiving neoadjuvant/adjuvant treatment with the FEC 100 regimen. Overall, less toxicity of any grade was observed in African American and more toxicity for Caucasian compared to Hispanic and Asian women. However, comparing non-haematologic toxicities especially of lesser severity retrospectively might be flawed as documentation may not accurately reflect the toxicity. Therefore, we have focused on comparing the haematologic toxicity that is more objective, as well as focusing on higher grade toxicity (grade 3 or higher) to decrease reporting bias.

The Asian patients experienced more frequent haematologic-related events including any grade. The two most common haematologic toxicities were febrile neutropenia and neutrophil nadir. However, race itself was not the significant predictor of overall higher toxicity. No significant differences were found in outcomes leading to dose delay, dose reduction, or hospitalisations due to this toxicity among the four different groups.

Some of studies have demonstrated that race might not entirely explain differences in pharmacogenetics or pharmacokinetics in chemotherapy agents, and these differences might be related to the individual variations, rather than grouping by different race/ethnic groups.[15]

Our study found that the main predictors of toxicity were low BMI <25 ($p = 0.033$, OR 0.4). Other studies have suggested that obese patients experience less toxicity from chemotherapy because they are undertreated commonly in current standard practices.[16,17] Although recent pharmacokinetic studies showed that actual body weight rather than ideal body weight should be used for chemotherapy dose calculations, physicians often use ideal body weight to calculate BSA or to cap

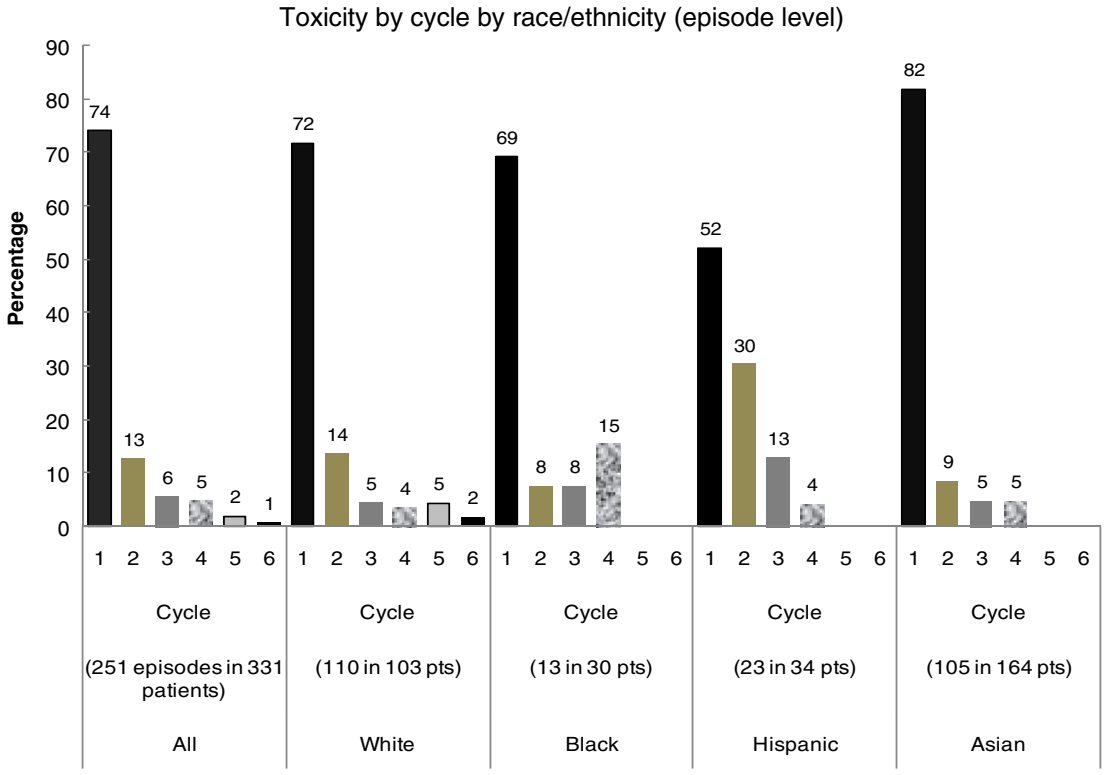

Fig. 1 – Toxicity by cycle and race/ethnicity (percentage relative to total episodes).

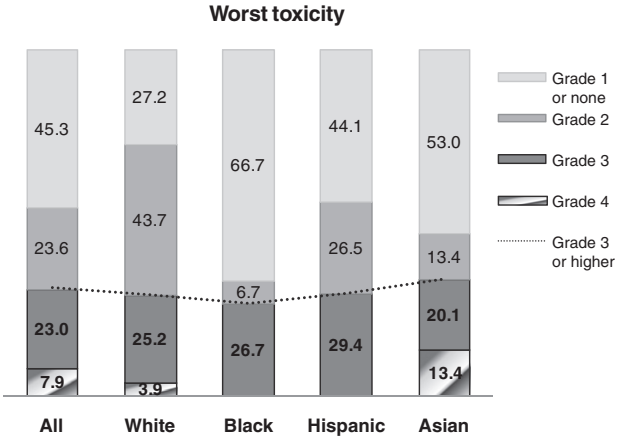

Fig. 2 – Distribution of worst grade toxicity overall and by race/ethnicity.

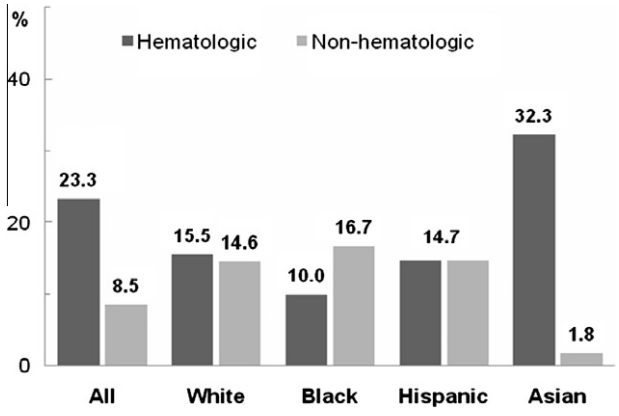

Fig. 3 – Grade 3 or higher toxicity by type, overall and by race and ethnicity.

the BSA at 2.0 among obese patients because of concern regarding excess toxicity in this patient population.[18] Total of 10 patients in our study (eight Caucasians, one Hispanic and one African American) had BSA > 2.2. None of Asian patients from Japan or Hong Kong had BSA > 2.2. All patients except three patients (one Caucasian, one Hispanic and one African American) received chemotherapy based on capped BSA at 2.0 (5 patients) or 2.2 (2 patients). This clinical practice might explain our finding of obese patients experiencing less toxicity than patients with lean or normal weight, which has been previously reported.[17]

In addition, data have shown a different clearance of chemotherapeutic agents in obese patients, for example, higher clearance of cisplatin and lower clearance of paclitaxel.[19] It is unclear whether 5-FU, epirubicin or cyclophosphamide is metabolised differently in obese patients; however, such a difference could explain our findings.

Comorbidities were identified in 28% of patients included in this study and hypertension was most common in 14% of patients. Comorbidity is often reported to be associated with increased toxicities during chemotherapy[20]; however, in our study, comorbidity did not significantly predict grade 3 or higher toxicity in multivariate analysis (Table 4). This may be due to the fact that this patient population was generally

Table 4 – Effect of potential predictors of grade 3 or higher toxicity.[a]

	Variable	Univariate		Multivariate	
		OR (95% CI)[c]	P	OR (95% CI)	P
Race	Black versus White	0.97 (0.34, 2.75)	0.959	1.29 (0.46, 3.61)	0.625
	Hispanic versus White	1.22 (0.45, 3.31)	0.701	1.52 (0.54, 4.33)	0.430
	Asian versus White	1.26 (0.74, 2.16)	0.394	1.03 (0.58, 1.81)	0.930
Age at diagnosis	⩾55 versus <55 years	0.88 (0.51, 1.49)	0.625	0.84 (0.48, 1.45)	0.525
Comorbidity	Yes versus No	0.94 (0.54, 1.66)	0.844	1.22 (0.66, 2.25)	0.524
Comorbidity	HTN/DM versus Other/None	0.97 (0.50, 1.84)	0.915	–	–
BMI[b]	25 to <30 versus <25	0.57 (0.31, 1.05)	0.072	0.54 (0.28, 1.02)	0.057
	⩾30 versus <25	0.47 (0.23, 0.98)	0.045	0.40 (0.17, 0.93)	0.033

[a] Logistic regression analysis based on 305 patients. In this analysis 26 patients were excluded due to missing value for any of the selected variables.
[b] Body mass index (kg/m^2): <18.5 (underweight), 18.5 to <25 (normal weight), 25 to <30 (overweight), ⩾30 (obese).
[c] OR = odds ratio, 95% CI: 95% confidence interval.

Table 5 – Effect of potential predictors of haematologic grade 3 or higher toxicity.[a]

	Variable	Univariate		Multivariate	
		OR (95% CI)[c]	P	OR (95% CI)	P
Race	Black versus White	0.30 (0.04, 2.47)	0.266	0.72 (0.14, 3.60)	0.689
	Hispanic versus White	0.98 (0.25, 3.81)	0.974	1.16 (0.29, 4.67)	0.833
	Asian versus White	2.28 (1.21, 4.31)	0.011	1.81 (0.92, 3.54)	0.085
Age at diagnosis	⩾55 versus <55	0.87 (0.48, 1.58)	0.655	0.86 (0.46, 1.61)	0.644
Comorbidity	Yes versus No	0.67 (0.34, 1.32)	0.247	1.05 (0.51, 2.18)	0.892
Comorbidity	HTN/DM versus Other/None	0.70 (0.32, 1.53)	0.371	–	
BMI[b]	25 to <30 versus <25	0.47 (0.23, 0.95)	0.035	0.59 (0.29, 1.22)	0.156
	⩾30 versus <25	0.27 (0.10, 0.71)	0.008	0.38 (0.13, 1.15)	0.086

[a] Logistic regression analysis on 280 patients. In this analysis 51 patients were excluded: 29 patients who had grade 3 or higher non-haematologic toxicity and 22 patients who had missing value for any of the selected variables.
[b] Body mass index (kg/m^2): <18.5 (underweight), 18.5 to <25 (normal weight), 25 to <30 (overweight), ⩾30 (obese).
[c] OR = odds ratio, 95% CI: 95% confidence interval.

healthy with good performance status and only mild/minor comorbidities.

There are several limitations in our multicenter study. The differences in patient numbers between cohorts had been recognised, especially the small numbers of African American and Hispanic women. Also, the retrospective nature of data collection and the differences in standard clinical practice across four different countries make it difficult to make a firm conclusion. However, our study clearly shows that that BMI and race may contribute to the tolerability to a cytotoxic regimen in the adjuvant setting. The results of this unique study have set a precedent for the need for future research in chemotherapy-related toxicity profiles among different racial and BMI groups. More research, particularly prospective studies that will include some biological correlates as well as pharmacokinetic data, and potentially pharmacogenomics using available advanced genomic techniques should be performed in order to optimise the use and delivery of chemotherapy and to identify the patients who are susceptible with increased toxicities from therapy. This research could then lead to improved long-term outcomes with improved tumour control and survival.

Conflict of interest statement

None declared.

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