Racial Disparities in Neutrophil Counts Among Patients with Metastatic Breast Cancer during Treatment with CDK4/6 Inhibitors

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Abstract

Purpose: The three CDK4/6 inhibitors (CDK4/6i) approved for use in HR-positive/HER2-negative metastatic breast cancer (MBC), palbociclib, ribociclib, and abemaciclib, are generally well tolerated but their most common toxicity is neutropenia. Within the general population, neutropenia has been shown to be more common in individuals of African descent. The landmark CDK4/6i trials in MBC lacked racial diversity in their patient populations. We aimed to assess the toxicity profiles of CDK4/6i in a racially diverse population.

Methods: We conducted a retrospective study at Montefiore Medical Center in patients with HR-positive/HER2-negative MBC prescribed CDK4/6i as first or subsequent lines of therapy between January 2015 and April 2020. Baseline characteristics and laboratory data at various treatment timepoints were collected.

Results: A total of 182 patients were included in the final analysis. Baseline absolute neutrophil count (ANC) was lower in the Black vs. Non-Black cohort ($p=0.001$) but the change in ANC from baseline (Delta-ANC) was smaller in the Black vs. Non-Black cohort and the ANC at different treatment timepoints was similar between groups. There was no difference in the rate of infection or number of dose delays or reductions between Black and Non-Black cohorts.

Conclusion: We analyzed toxicity profiles of 182 patients with HR-positive/HER2-negative MBC treated with CDK4/6i. Our population included 46% Black patients, who were found to have a lower baseline ANC but no increase in complications. Despite the lower baseline ANC seen in our Black cohort prior to starting CDK4/6i, treatment toxicities were similar between racial groups.

Introduction

Cyclin dependent kinases (CDKs) play an important role in cell cycle physiology. CDK4 and CDK6 are involved in the G1 phase of the cell cycle and interact with D-type cyclins, particularly Cyclin D1, which forms complexes with CDK4 and CDK6. Activation of the cyclin D1-CDK4/6 complex phosphorylates the tumor suppressor retinoblastoma protein (RB), leading to EF2 release and transition of the cell cycle from G1 to S phase [1, 2]. Estrogens can induce cellular expression of Cyclin D1 leading to activation of the CDK4/6 RB pathway, thereby promoting cell cycle progression [1–3]. In-vitro studies of CDK4/6 inhibitors (CDK4/6i) in human breast cancer cell lines reported that sensitivity varied based on molecular phenotype [4, 5]. Hormone positive cell lines, which usually retain functional RB1, were found to be the most sensitive; moreover, there was synergy when combined with tamoxifen [5]. This work led to the phase 2 PALOMA-1 trial evaluating the CDK4/6i palbociclib in combination with antiestrogen therapy as first line treatment in hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC), resulting in approval of the first CDK4/6i palbociclib by the U.S. Food and Drug Administration (FDA) in 2015 [6]. Subsequent studies led to FDA approval of ribociclib and abemaciclib for this same indication. All three drugs are approved in combination with aromatase

inhibitors and with the selective estrogen receptor degrader, fulvestrant. Specificity of these drugs in targeting CDK4/6 is critical for establishing a therapeutic window through preferential inhibition of oncogenic events without significant toxicity in normal tissue [7].

CDK4/6i are well tolerated and adverse events are usually managed with dose modification and supportive care measures. Hematologic toxicities are common, with neutropenia being the dose-limiting toxicity for palbociclib and ribociclib. Neutropenia is rapidly reversible, reflecting a cytostatic effect on bone marrow precursors. Therefore, palbociclib and ribociclib are dosed intermittently to allow a break for hematologic recovery. Abemaciclib commonly exhibits gastrointestinal side effects, whereas neutropenia is less evident [8].

Neutrophils comprise most circulating leukocytes and serve a critical antimicrobial role [9]. Asymptomatic reductions in peripheral blood neutrophil counts are often observed in individuals of African descent, with a prevalence of 10-30% [10]. In the U.S., Black individuals have lower neutrophil counts than White individuals (mean difference 0.83×10^9 cells/L) and higher rates of neutropenia (4.5% vs. 0.79%) [11, 12]. Although the etiology is not entirely clear, studies have identified a chromosome 1q22 polymorphism containing the Duffy antigen and receptor for chemokine (DARC) gene which strongly influences leukocyte counts in African Americans and is one potential mechanism [13].

Most patients enrolled in the CDK4/6i breast cancer clinical trials were White, leaving us with limited data on the effect of CDK4/6i on neutrophil counts in Black patients. In this study, we aimed to assess the impact of CDK4/6i on neutrophil counts in Black patients and compare the neutrophil counts between Black and Non-Black patients throughout their treatment course. We also aimed to evaluate toxicity profiles and breast cancer outcomes stratified by race in patients receiving CDK4/6i.

Methods

Study design and data collection

We conducted a single-center retrospective study at Montefiore Medical Center. Using the institutional clinical software, “Clinical Looking Glass”, we identified patients with HR-positive, HER2-negative MBC who were prescribed a CDK4/6i as first or subsequent lines of therapy between January 1st, 2015 and April 28th, 2020. We excluded patients with inaccessible medical records, patients whose race was not available, patients who were lost to follow up, patients who did not take the prescribed CDK4/6i, those treated at outside institutions, and those who were treated with CDK4/6i for less than 14 days. Baseline characteristics such as age, race, ethnicity, and information on prior treatment lines for metastatic disease were collected through chart review. Other data including tumor grade, the presence of visceral involvement, and menopausal status were also collected. The Standard Charlson Comorbidity Index was calculated for each patient included in the study.

Race was defined as Black, White, Asian, or Other. Laboratory data including complete metabolic panels at baseline and during each month of CDK4/6i treatment were collected from the medical records. Complete blood count data were collected at cycle 1, day 1 (C1D1); cycle 1, day 14 (C1D14); cycle 2, day 1 (C2D1); cycle 2, day 14 (C2D14); cycle 3, day 1 (C3D1); cycle 4, day 1 (C4D1); cycle 5, day 1 (C5D1); and cycle 6, day 1 (C6D1). All oncology clinic and hospital admission notes during the time that patients were receiving CDK4/6i were reviewed and scrutinized for information regarding treatment response and adverse events.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. The Pearson's Chi-square test or Fisher's exact test was used to assess associations between two categorical variables. The Wilcoxon rank sum test was used to compare neutrophil counts at each time point between Black vs. Non-Black patients. Change in neutrophil count over time was compared using the Wilcoxon signed rank sum test.

Adverse events were recorded in our database and were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The number of dose reductions or dose delays was also recorded. The Pearson's Chi-square test was used to compare adverse event rates between Black vs. Non-Black patients.

Progression free survival (PFS) was calculated as the time in days between the date of CDK4/6i initiation and the date of disease progression or death. Data was censored at the date each patient was last seen at our institution. The Kaplan-Meier method was used to estimate PFS, and the log-rank test was used to compare PFS between groups. To assess the effect of neutropenia and dose reduction on PFS, a landmark analysis was conducted excluding patients who died or had disease progression within 28 days of CDK4/6i initiation. Multivariable Cox Proportional-Hazards model, adjusting for age, visceral disease, menopausal status, CDK4/6i as first line therapy, and development of neutropenia, was used to compare the PFS between Black and Non-Black patients. Statistical analysis was conducted using STATA version 14.0 and R statistical software. This study was approved by the Albert Einstein Institutional Board Review.

Results

Baseline Characteristics

A total of 233 patients were identified. Of those, 45 patients were excluded for the following reasons: 11 were treated at outside institutions, 4 were lost to follow up, 13 never took the prescribed CDK4/6i, 2 had HER2+ disease, 6 had inaccessible medical records, 8 were treated with CDK4/6i for less than 14 days, and 1 patient did not have stage IV disease. Out of the 188 remaining evaluable patients, an additional 6 patients were excluded as there were no data available on their race (Figure 1). Our final cohort included 182 patients with a median age of 64 years [interquartile range (IQR), 54-72]. There were 61 Hispanic

(34%) and 121 non-Hispanic (66%) patients. Most patients (77%) were postmenopausal and 67% had visceral metastases. CDK4/6i was used as first line therapy in 88 patients (48%). Palbociclib was the most commonly used CDK 4/6i accounting for 153 patients (84%). Ribociclib and abemaciclib were prescribed in 9 (5%) and 20 (11%) patients, respectively. Most patients had not received prior chemotherapy (79%) or prior endocrine therapy (54%) for metastatic disease. Letrozole, fulvestrant, and anastrozole were prescribed in 88 (48%), 68 (37%), and 19 (10%) patients, respectively. The most common reason for CDK4/6i discontinuation was progression of disease (94 patients, 82%), whereas neutropenia was responsible for drug discontinuation in only 2 patients (2%).

In our cohort, 83 patients (46%) were Black, 39 (21%), 10 (5%), and 50 (27%) patients were White, Asian, and Other race, respectively. For the purpose of comparison, we consolidated all the Non-Black patients into one group. Hispanics accounted for 8% of patients in the Black cohort and 55% in the Non-Black cohort ($p<0.01$). Baseline characteristics were similar between Black and Non-Black groups with no significant difference in median age (64 vs. 63 years, $p=0.47$), postmenopausal status (75% vs. 80%, $p=0.67$), or visceral metastases (67% vs 67%, $p>0.99$). CDK4/6i were used in the first line for metastatic disease in 48% of patients in both groups. All three CDK4/6i were used in a similar proportion between the Black and Non-Black cohorts ($p=0.28$). The endocrine therapy backbones were similar between Black and Non-Black groups as well ($p=0.67$), (Table 1).

Table 1
Baseline Characteristics

	All Patients (n=182)	Black (n=83)	Non- Black (n=99)	P- value
Age, year, No. (%)	64	64	63	0.47
Median	54-72	55-73.5	53.5-72	
IQR				
Ethnicity, No. (%)	61 (34%)	7 (8%)	54 (55%)	<0.001
Hispanic	121 (66%)	76 (92%)	45 (45%)	
Non-Hispanic				
Race, No. (%)	83 (46%)			
Black	39 (21%)			
White	10 (5%)			
Asian	50 (27%)			
Other				
Menopausal status, No. (%)	28 (15%)	14 (17%)	14 (14%)	0.67
Premenopausal	5 (3%)	3 (4%)	2 (2%)	
Perimenopausal	141 (77%)	62 (75%)	79 (80%)	
Postmenopausal	8 (4%)	4 (5%)	4 (4%)	
Unknown				
Charlson Comorbidity Index (CCI)	8.0	8.0	8.0	0.21
Median	7.0 – 10.0	7.0 – 10.0	7.0 – 9.0	
IQR				
Tumor grade, No. (%)	7 (4%)	2 (2%)	5 (5%)	0.61
Well differentiated	50 (27%)	24 (29%)	26 (26%)	
Moderately differentiated	55 (30%)	24 (29%)	31 (31%)	
Poorly differentiated	70 (38%)	33 (40%)	37 (37%)	
Unknown				

	All Patients (n=182)	Black (n=83)	Non- Black (n=99)	P- value
Sites of metastases, No. (%)	59 (32%)	27 (33%)	32 (32%)	>0.99
Non Visceral	122 (67%)	56 (67%)	66 (67%)	
Visceral	1 (1%)	0 (0%)	1 (1%)	
Unknown				
Prior chemotherapy lines for metastatic disease, No. (%)	143 (79%)	67 (81%)	76 (77%)	0.56
0	24 (13%)	10 (12%)	14 (14%)	
1	7 (4%)	4 (5%)	3 (3%)	
2	3 (2%)	1 (1%)	2 (2%)	
3	0 (0%)	0 (0%)	0 (0%)	
4	1 (1%)	0 (0%)	1 (1%)	
5	1 (1%)	0 (0%)	1 (1%)	
6	3 (2%)	1 (1%)	2 (2%)	
Unknown				
Prior endocrine therapy lines for metastatic disease, No. (%)	99 (54%)	45 (54%)	54 (55%)	0.96
0	39 (21%)	18 (22%)	21 (21%)	
1	22 (12%)	13 (16%)	9 (9%)	
2	8 (4%)	2 (2%)	6 (6%)	
3	5 (3%)	1 (1%)	4 (4%)	
4	3 (2%)	1 (1%)	2 (2%)	
5	2 (1%)	1 (1%)	1 (1%)	
6	1 (1%)	1 (1%)	0 (0%)	
7	3 (2%)	1 (1%)	2 (2%)	
Unknown				

	All Patients (n=182)	Black (n=83)	Non- Black (n=99)	P- value
CDK4/6i in first line setting for metastatic disease, No. (%)	91 (50%)	42 (51%)	49 (49%)	>0.99
No	88 (48%)	40 (48%)	48 (48%)	
Yes	3 (2%)	1 (1%)	2 (2%)	
Unknown				
Endocrine therapy backbone, No. (%)	88 (48%)	43 (52%)	45 (45%)	0.67
Letrozole	19 (10%)	6 (7%)	13 (13%)	
Anastrozole	5 (3%)	3 (4%)	2 (2%)	
Exemestane	68 (37%)	30 (36%)	38 (38%)	
Fulvestrant	2 (1%)	1 (1%)	1 (1%)	
Tamoxifen				
CDK 4/6i, No. (%)	153 (84%)	70 (84%)	83 (84%)	0.28
Palbociclib	20 (11%)	7 (8%)	13 (13%)	
Abemaciclib	9 (5%)	6 (7%)	3 (3%)	
Ribociclib				
Reason for CDK4/6i discontinuation, No. (%)	94 (82%)	47 (82%)	47 (82%)	>0.99
Progression of disease (POD)	2 (2%)	1 (2%)	1 (2%)	
Neutropenia	2 (2%)	1 (2%)	1 (2%)	
Infection	16 (14%)	8 (14%)	8 (14%)	
Other				
Cause of death, No. (%)	18 (10%)	11 (13%)	7 (7%)	0.65
Breast cancer	4 (2%)	3 (4%)	1 (1%)	
Other	1 (1%)	1 (1%)	0 (0%)	
Unknown				

Neutrophil and white blood cell count at baseline and over time

The baseline (C1D1) median absolute neutrophil count (ANC) was lower in the Black vs. Non-Black cohort (3.0 vs. $4.0 \times 10^9/L$, $p=0.001$), with similar results at C3D1 (1.40 vs. $1.75 \times 10^9/L$, $p=0.03$). However, there was no significant difference in median ANC between Black and Non-Black cohorts at C1D14 (1.15 vs. $1.30 \times 10^9/L$, $p=0.07$), C2D1 (1.2 vs. $1.3 \times 10^9/L$, $p=0.40$), and C2D14 (1.65 vs. $1.5 \times 10^9/L$, $p=0.38$) (Table 2). When the change in ANC from baseline was calculated (Delta-ANC), Black patients showed a smaller decrease in median ANC over time compared to Non-Black patients. Delta-ANC at C2D1 was -1.5 vs. $-2.6 \times 10^9/L$ ($p=0.001$), for Black vs. Non-Black cohorts, respectively, and delta-ANC at C3D1 was -1.5 vs. $-2.4 \times 10^9/L$ ($p=0.007$) for Black vs. Non-Black patients, respectively (Table 2; Figure 2). White blood cell count (WBC) showed a similar pattern. The baseline WBC (C1D1) was lower in the Black compared to Non-Black cohort (5.5 vs. $6.6 \times 10^9/L$, $p=0.001$). Black patients also experienced a smaller decrease in WBC over time as compared with Non-Black patients. Delta-WBC at C2D1 was -1.95 vs. $-3.3 \times 10^9/L$ ($p=0.003$) for Black vs. Non-Black patients, and delta-WBC at C3D1 was -1.9 vs. $-2.9 \times 10^9/L$ ($p=0.005$) for Black and Non-Black patients, respectively (Table 7; Figure 6).

Table 2
Neutrophil Count Over Time in Black vs. Non-Black Cohorts

All Patients (n=182)	Black (n=83)	Non -Black (n=99)	P-value
ANC C1D1	3.0	4.0	0.001
Median	2.4 – 4.6	3.15 – 5.1	
IQR			
ANC C1D14	1.15	1.3	0.07
Median	0.8 – 1.72	1.0 – 2.18	
IQR			
ANC C2D1	1.2	1.3	0.40
Median	0.9 – 1.72	0.9 – 1.9	
IQR			
ANC C2D14	1.65	1.5	0.38
Median	1.2 – 2.6	1.1 – 2.3	
IQR			
ANC C3D1	1.4	1.75	0.03
Median	1.0 – 2.0	1.2 – 2.6	
IQR			
Δ ANC C1D14	-1.65	-2.45	0.03
Median	-3.12 – -1.05	-3.4 – -1.62	
IQR			
Δ ANC C2D1	-1.5	-2.6	0.001
Median	-2.45 – -0.8	-3.3 – -1.6	
IQR			
Δ ANC C2D14	-1.7	-2.25	0.15
Median	-2.7 – -0.7	-3.02 – -1.28	
IQR			
Δ ANC C3D1	-1.5	-2.4	0.007
Median	-2.4 – -0.8	-3.18 – -1.23	
IQR			

Neutropenia

Most patients (86%) experienced neutropenia, with grade 1, grade 2, grade 3, and grade 4 neutropenia reported in 10%, 24%, 43%, and 8% of patients, respectively (Table 3). Among Black patients, the rates of grade 1, grade 2, grade 3, and grade 4 neutropenia were 11%, 17%, 51%, and 12%, respectively, whereas those rates for Non-Black patients were 10%, 29%, 37%, and 5%, respectively (Table 3). There was a statistically significant difference in neutropenia rates between Black and Non-Black cohorts ($p=0.04$).

Table 3
All Toxicities in Black vs. Non-Black Cohorts

	All Patients (n=182)	Black (n=83)	Non-Black (n=99)	P-value
Any Adverse Event	182 (100%)	83 (100%)	99 (100%)	0.23
Neutropenia, No. (%)	156 (86%)	75 (90%)	81 (82%)	0.04
Any grade	19 (10%)	9 (11%)	10 (10%)	
Grade 1	43 (24%)	14 (17%)	29 (29%)	
Grade 2	79 (43%)	42 (51%)	37 (37%)	
Grade 3	15 (8%)	10 (12%)	5 (5%)	
Grade 4				
Fatigue, No. (%)	44 (24%)	17 (20%)	27 (27%)	0.44
Any grade	36 (20%)	14 (17%)	22 (22%)	
Grade 1	5 (3%)	1 (1%)	4 (4%)	
Grade 2	3 (2%)	2 (2%)	1 (1%)	
Grade 3				
Anemia, No. (%)	95 (52%)	40 (48%)	55 (56%)	0.25
Any grade	60 (33%)	23 (28%)	37 (37%)	
Grade 1	21 (12%)	8 (10%)	13 (13%)	
Grade 2	14 (8%)	9 (11%)	5 (5%)	
Grade 3				
Thrombocytopenia, No. (%)	86 (47%)	37 (45%)	49 (49%)	0.42
Any grade	73 (40%)	32 (39%)	41 (41%)	
Grade 1	5 (3%)	1 (1%)	4 (4%)	
Grade 2	6 (3%)	2 (2%)	4 (4%)	
Grade 3	2 (1%)	2 (2%)	0 (0%)	
Grade 4				
Nausea, No. (%)	22 (12%)	7 (8%)	15 (15%)	0.18
Any grade	22 (12%)	7 (8%)	15 (15%)	
Grade 1				

	All Patients (n=182)	Black (n=83)	Non-Black (n=99)	P-value
Diarrhea, No. (%)	19 (10%)	5 (6%)	14 (14%)	0.19
Any grade	14 (8%)	4 (5%)	10 (10%)	
Grade 1	3 (2%)	0 (0%)	3 (3%)	
Grade 2	2 (1%)	1 (1%)	1 (1%)	
Grade 3				
Rash, No. (%)	10 (5%)	6 (7%)	4 (4%)	0.51
Any grade	10 (5%)	6 (7%)	4 (4%)	
Grade 1				
Infections^a, No. (%)	32 (18%)	11 (13%)	21 (21%)	0.22
Number of infections				
Decreased Appetite, No. (%)	25 (14%)	13 (16%)	12 (12%)	0.75
Any grade	23 (13%)	12 (14%)	11 (11%)	
Grade 1	2 (1%)	1 (1%)	1 (1%)	
Grade 2				
Headache, No. (%)	10 (5%)	2 (2%)	8 (8%)	0.11
Any grade	10 (5%)	2 (2%)	8 (8%)	
Grade 1				
Arthralgias, No. (%)	13 (7%)	5 (6%)	8 (8%)	0.77
Any grade	13 (7%)	5 (6%)	8 (8%)	
Grade 1				
Hot flush, No. (%)	11 (6%)	6 (7%)	5 (5%)	0.55
Any grade	11 (6%)	6 (7%)	5 (5%)	
Grade 1				

Infections

Infections were seen in 32 patients (18%), with no difference in the rate of infection between Black vs. Non-Black patients (13% vs. 21%, p=0.22) (Table 3). Of note, there were 3 Black patients (4%) and 7 Non-Black patients (7%) who had more than one infection. Among Black patients, there were a total of 14

infections [pneumonia (n=4), urinary tract infection (n=2), bacteremia (n= 2), febrile neutropenia (n=2), and other (n=4)]. In Non-Black patients, there were a total of 28 infections [urinary tract infection (n=6), upper respiratory infection (n=5), pneumonia (n=3), osteomyelitis (n=3), skin infection (n=6), and other (n=5)]. Grade 1, grade 2, grade 3, and grade 4 infections were present in 0, 4, 7, and 3 Black patients and 3, 14, 10, and 1 Non-Black patients, respectively (Table 8).

Other Toxicities

There was no difference in the rate of thrombocytopenia in the Black vs. Non-Black cohort (45% vs. 49%, $p=0.42$) (Table 3). Grade 1/2 thrombocytopenia rates were 40% and 45% for the Black and Non-Black group, respectively, whereas grade 3/4 thrombocytopenia was present in 4% of patients in both groups. There was also no statistically significant difference in the rate of anemia for Black vs. Non-Black cohorts (48% vs. 56%, $p=0.25$). Grade 3 anemia was present in 11% vs. 5% in Black vs. Non-Black, whereas the rates of grade 1/2 anemia were 38% and 50%, respectively (Table 3). Commonly reported gastrointestinal toxicities were nausea, diarrhea, and decreased appetite. Nausea was present in 8% and 15% in Black and Non-Black groups ($p=0.18$), respectively, and all those events were grade 1. The rate of diarrhea was 6% vs. 14% in Black vs. Non-Black groups ($p=0.19$), respectively, and decreased appetite was present in 16% vs 12% in Black vs. Non-Black groups ($p=0.75$) (Table 3).

Dose reductions and delays

At least one dose reduction was required in 53 patients (29%); 39 patients required one dose reduction while 14 patients required more than one dose reduction (Table 4). Black patients required more dose reductions than Non-Black patients, but this difference was not statistically significant (34% vs. 25%, $p=0.27$). One dose reduction was required in 22 Black and 17 Non-Black patients, whereas more than one dose reduction was required in 6 Black and 8 Non-Black patients. Dose delay was required in 61 patients (34%); 29 patients required one dose delay, while 32 patients required more than 1 dose delay. There was no difference in the rate of dose delay between Black vs. Non-Black patients (36% vs. 31%, $p=0.59$). One dose delay was required in 13 Black patients and 16 Non-Black patients, whereas more than one dose delay was required in 17 Black and 15 Non-Black patients. Both a dose reduction and delay was required in 26% of patients; with no difference between Black and Non-Black patients (33% vs. 21%, $p=0.11$). In our entire cohort, 36% of patients required either a dose reduction or dose delay, with similar rates for Black and Non-Black patients (37% vs. 35%, $p=0.90$) (Table 4).

Table 4
Patients who Required Either Dose Reductions or Dose Delays

	All patients (n=182)	Black (n=83)	Non-Black (n=99)	P-value
Dose reductions, No. (%)	53 (29%)	28 (34%)	25 (25%)	0.27
Any dose reduction	39 (21%)	22 (27%)	17 (17%)	
1 Dose reduction	11 (6%)	6 (6%)	6 (6%)	
2 Dose reductions	3 (2%)	5 (6%)	2 (2%)	
3 Dose reductions		1 (1%)		
Dose delays, No. (%)	61 (34%)	30 (36%)	31 (31%)	0.59
Any dose delay	29 (16%)	13 (16%)	16 (16%)	
1 Dose delay	12 (7%)	6 (6%)	6 (6%)	
2 Dose delays	10 (6%)	6 (7%)	5 (5%)	
3 Dose delays	5 (3%)	5 (6%)	2 (2%)	
4 Dose delays	1 (1%)	3 (4%)	0 (0%)	
5 Dose delays	4 (2%)	1 (1%)	2 (2%)	
>5 Dose delays		2 (2%)		
Dose reduction and delay, No. (%)	48 (26%)	27 (33%)	21 (21%)	0.11
Any dose modification; reduction or delay, No. (%)	66 (36%)	31 (37%)	35 (35%)	0.90

CDK4/6 inhibitor discontinuation

CDK4/6i were discontinued in 114 patients, and the most common reason for this was progression of disease (n=94). Among Black patients, the most common reasons for CDK 4/6i discontinuation were progression of disease (n=47), other (n=8), infection (n=1), and neutropenia (n=1). Among Non-Black patients, the most common reasons for discontinuation were progression of disease (n=47), other (n=8), infection (n=1), and neutropenia (n=1) (Table 1).

Progression-free survival

There was no difference in median PFS between Black and Non-Black groups (316 vs. 407 days, p=0.51) (Figure 3, Table 5). Among patients who received CDK4/6i as first line treatment, the median PFS for

Black and Non-Black patients were 390 and 518 days ($p=0.48$), respectively (Table 5). We also assessed breast cancer outcomes stratified by neutropenia, to evaluate whether the drug's effects on the bone marrow could predict disease response. Among patients who developed neutropenia, the median PFS was 336 vs. 421 days ($p=0.45$) for Black and Non-Black groups, respectively (Table 5; Figure 4). Whereas in those without neutropenia, the median PFS was 141 and 259 days ($p=0.46$) for Black and Non-Black patients, respectively (Table 5; Figure 8).

Table 5
Median PFS in Black vs. Non-Black Cohorts

	Black (n=83)	Non-Black (n=99)	P- value
PFS (days), [95% CI]	316 [205, 512]	407 [325, 598]	0.51
PFS (days), [95% CI] in the first line setting	390 [312, NR]	518 [401, NR]	0.48
PFS (days), [95% CI] in patients without neutropenia	141 [104, NR]	259 [122, NR]	0.46
PFS (days), [95% CI] in patients with neutropenia	336 [221, 687]	421 [325, 616]	0.45
PFS (days), [95% CI] in the first line and with neutropenia	390 [312, NR]	518 [401, NR]	0.45
PFS (days), [95% CI] without dose reduction	346 [205, 796]	377 [294, 518]	0.91
PFS (days), [95% CI] with dose reduction	312 [121, NR]	627 [294, NR]	0.26
PFS (days), [95% CI] with dose reduction in the first line setting	316 [223, NR]	627 [407, NR]	0.28

Next, we assessed the effect of dose reductions on breast cancer outcomes by racial groups. Among patients who required a dose reduction, the median PFS was 312 vs. 627 days ($p=0.26$) for Black vs. Non-Black patients (Table 5; Figure 5). While in those without dose reduction the median PFS was 346 vs. 377 days ($p=0.91$) for Black and Non-Black groups, respectively (Table 5; Figure 9).

In a univariate analysis, CDK4/6i as first line therapy ($p=0.02$) and presence of visceral disease ($p=0.04$) were statistically significantly associated with PFS, while Black race ($p=0.51$), neutropenia ($p=0.09$), and age ($p=0.27$) were not associated with PFS (Table 6). We then created a multivariable analysis using Cox Proportional-Hazards model including Black race, neutropenia, age, visceral status, and CDK4/6i as first line therapy. In this model, Black race, neutropenia, and age were not associated with PFS. CDK4/6i as

first line therapy was positively associated with PFS (HR 0.59, 95% CI 0.38-0.90, p=0.01), whereas visceral metastasis was inversely associated with PFS (HR 1.67, 95% CI 1.02-2.70, p=0.04) (Table 6).

Table 6
Univariate and Multivariable Analysis of PFS by Cox Regression Model

Characteristic	Reference	Univariate			Multivariable		
		HR	95% CI	P values	HR	95% CI	P-value
Age	-	0.99	(0.97-1.00)	0.27	0.99	(0.97-1.0)	0.20
Black Race	Non-Black	1.14	(0.74-1.53)	0.51	1.17	(0.77-1.8)	0.46
Visceral involvement	None	1.62	(1.14-2.08)	0.04	1.67	(1.02-2.7)	0.04
Any neutropenia	No neutropenia	0.57	(-0.03-1.18)	0.09	0.72	(0.36-1.4)	0.35
First line treatment	Not first line	0.64	(0.19-1.01)	0.02	0.59	(0.38-0.9)	0.01

Discussion

Neutropenia is the most common adverse event reported in CDK4/6i landmark trials [6, 14–22]. In the PALOMA-2 trial, neutropenia was seen in 80% of patients in the palbociclib group, and grade 3/4 neutropenia was seen in 66% [14]. Similar results were seen in the MONALEESA and MONARCH trials which studied the use of ribociclib and abemaciclib, respectively [15, 16, 18, 19, 21, 22]. Neutropenia is most common with palbociclib and ribociclib. In contrast, abemaciclib causes less neutropenia but more diarrhea and fatigue due to its stronger selectivity for CDK4 which is less involved in hematopoiesis than CDK6 [2, 23]. CDK6 regulates cytokine expression in hematopoiesis [24], contributes to the “control” of myeloid progenitor expansion, and plays many important roles in myeloid differentiation [25]. Most data about CDK4 and CDK6 are derived from total knockout mouse models which can develop hematological compensatory mechanisms starting in embryogenesis. Maurer et al. generated transgenic mice that lack either CDK4 or CDK6 in adult hematopoiesis to study direct consequences of CDK4 or CDK6 loss in adult mice, mirroring the effect of CDK4/6i. Deletion of CDK6 in adult hematopoiesis affected all stem cell fractions and led to neutropenia, while deletion of CDK4 resulted in elevated numbers of myeloid progenitors without translating into numeric changes of differentiated myeloid cells [26].

An ANC $< 1.5 \times 10^9/L$ has been used to define grade 2 toxicity per the CTCAE version 5.0 and is often used as a cutoff value for inclusion in oncology clinical trials [27, 28]. Population studies show that Black

patients in the U.S. have lower mean neutrophil counts and a higher prevalence of neutropenia compared to Non-Black patients [11]. Benign ethnic neutropenia (BEN), an entity in which an ANC of less than $1.5 \times 10^9/L$ is seen in certain populations, is most common in people of African descent [27]. Although BEN has not been associated with an increased risk of systemic infection or febrile neutropenia, a proportion of patients with BEN may be inadvertently excluded from oncology clinical trials or have unnecessary dose interruptions and reductions, due to their lower than normal pre-treatment neutrophil counts [27]. Indeed, few Black patients were included in CDK4/6i clinical trials. PALOMA-2 included 11 Black patients (3.2%), PALOMA-3 included 29 Black patients (6%), MONALEESA-3 included 5 Black patients (1.4%), and MONALEESA-7 included 19 Black patients (6%) [14, 15, 18, 19, 22]. Our study has the largest proportion of Black patients (46%; N=83) reported in the literature in this clinical scenario, which allowed us to be the first study to evaluate racial disparities in toxicities and breast cancer outcomes for patients treated with CDK4/6i for advanced breast cancer.

Prior studies have evaluated racial disparities in neutrophil counts in breast cancer patients receiving chemotherapy. Smith et al. found no racial differences in the frequency of febrile neutropenia in breast cancer patients receiving chemotherapy, despite a lower baseline ANC in Black patients [29]. A retrospective analysis by Hershman et al. found that Black patients had a lower baseline WBC prior to starting adjuvant chemotherapy and after completing treatment but had a similar mean percentage decline in WBC from baseline to treatment completion compared to White patients [30]. In another study analyzing differences in WBC counts and dose delays/discontinuations between Black and White breast cancer patients receiving adjuvant chemotherapy from two clinical trials, there was no difference between races in the number of patients who experienced neutropenic fever, despite a lower baseline WBC and ANC in the Black group [31]. These studies call into question the clinical relevance of a lower baseline WBC and ANC that may be seen in Black patients, and whether clinical trial inclusion criteria should more frequently be liberalized.

Inclusion criteria for most CDK4/6i landmark trials required an ANC $\geq 1.5 \times 10^9/L$, which may have impacted the underrepresentation of Black patients in these studies [14, 17, 21, 22, 32]. The phase 2 single arm PALINA trial analyzed the hematologic safety of palbociclib in combination with letrozole or fulvestrant in self-reported African American, African, or Black women with HR-positive/HER2-negative MBC [32]. Inclusion criteria was an ANC cutoff of $1.0 \times 10^9/L$. The study enrolled 35 patients and the median baseline ANC was $3.1 \times 10^9/L$. None of the patients experienced febrile neutropenia or required drug discontinuation due to neutropenia. Lower baseline ANC (2.4 vs $4.3 \times 10^9/L$, $p=0.006$), grade 3 neutropenia (66.7% vs. 23%, $p=0.029$), and dose reductions (55.6% vs. 7.7%, $p=0.008$) were more common in patients found to have the Duffy null polymorphism [32]. Interestingly, our study reports similar results as the PALINA trial, that CDK4/6i may be administered safely in Black patients even if they have a lower baseline ANC.

We report that Black patients have a lower baseline ANC (3.0 vs. $4.0 \times 10^9/L$, $p=0.001$), and smaller decreases in ANC over time compared to Non-Black patients (delta-ANC at C2D1 was -1.5 vs. $-2.6 \times 10^9/L$,

p=0.001) while on treatment with CDK4/6i. Despite this, Black patients had similar infection rates compared to Non-Black patients (13% vs. 21%, p=0.22). Our study is the first to elucidate that despite lower baseline neutrophil counts seen in Black patients, there are no differences between racial groups in the frequency of infections, dose reductions, or dose delays seen with CDK4/6i use in MBC. Based on these results, the lower baseline neutrophil counts that may be seen in Black patients should not cause concern or hesitancy when initiating CDK4/6i.

Conclusion

In our cohort, Black patients had a lower baseline ANC compared to Non-Black patients, but they experienced less of a decline in ANC from baseline (delta-ANC) during treatment with CDK4/6i. Our results are the first to examine racial disparities in toxicities in patients receiving CDK4/6i. Our data suggest that CDK4/6i can be safely administered in patients who may have BEN, since their baseline ANC does not necessarily translate into increased rates of infections, dose reductions, or dose delays.

Declarations

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Competing Interests

Ashley B. Weiner: This author has no relevant financial or non-financial interests to disclose

Laura Munoz-Arcos: This author has no relevant financial or non-financial interests to disclose

Alvaro Alvarez: This author has no relevant financial or non-financial interests to disclose

Joseph A. Sparano: This author has no relevant financial or non-financial interests to disclose

Jesus D. Anampa: This author has no relevant financial or non-financial interests to disclose

Author Contributions

All authors contributed to the study conception and design as well as material preparation, data collection and analysis. The first draft of the manuscript was written by Ashley Weiner and Jesus Anampa and all authors commented on previous versions of the manuscript. All authors have read and approve the final manuscript.

Ethics Approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Montefiore Medical Center/Einstein College of Medicine approved this study.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Consort Diagram

Consort diagram: A total of 233 patients were initially identified and 51 patients were excluded, leaving 182 patients in the final analysis

Figure 2

Neutrophil Count Over Time in Black vs. Non-Black Cohorts

Neutrophil count over time while on treatment with CDK4/6 inhibitors in Black vs. Non-Black patients. Abbreviations: C1D1: Cycle 1 Day 1; C1D14: Cycle 1 Day 14; C2D1: Cycle 2 Day 1; C2D14: Cycle 2 Day 14; C3D1: Cycle 3 Day 1; C4D1: Cycle 4 Day 1; C5D1: Cycle 5 Day 1; C6D1: Cycle 6 Day 1.

Figure 3

PFS in Black vs. Non-Black Cohorts

PFS compared between Black vs. Non-Black cohorts expressed in days. The yellow line represents the Non-

Black cohort and the blue line represents the Black cohort. Abbreviations: PFS: Progression Free Survival.

Figure 4

PFS in Patients with Neutropenia in Black vs. Non-Black

PFS expressed in days in patients who experienced neutropenia while on CDK4/6 inhibitor treatment, compared

between the Black vs Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line

represents the Black cohort. Abbreviations: PFS: Progression Free Survival.

PFS by Race- Patients with dose reduction

Figure 5

PFS in Patients with Dose Reductions in Black vs. Non-Black Cohorts

PFS expressed in days in patients who required a dose reduction while on treatment with CDK4/6 inhibitors, compared between the Black vs Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort Abbreviations: PFS: Progression Free Survival.

Figure 6

White Blood Cell Count Over Time in Black vs. Non-Black Cohorts

White blood cell count over time while on treatment with CDK4/6 inhibitors in Black vs. Non-Black patients. Abbreviations: C1D1: Cycle 1 Day 1; C1D14: Cycle 1 Day 14; C2D1: Cycle 2 Day 1; C2D14: Cycle 2 Day 14; C3D1: Cycle 3 Day 1; C4D1: Cycle 4 Day 1; C5D1: Cycle 5 Day 1; C6D1: Cycle 6 Day 1.

Figure 7

PFS in Patients on First Line Treatment in Black vs. Non-Black Cohorts

PFS expressed in days in patients on first line treatment with CDK4/6 inhibitors, compared between the Black vs. Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort. Abbreviations: PFS: Progression Free Survival.

Figure 8

PFS in Patients Without Neutropenia in Black vs. Non-Black Cohorts

PFS expressed in days in patients who did not experience neutropenia while on treatment with CDK4/6 inhibitors, compared in the Black vs. Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort. Abbreviations: PFS: Progression Free Survival.

Figure 9

PFS in Patients without dose reduction, Black vs. Non-Black

PFS expressed in days in patients who did not require a dose reduction while on treatment with CDK4/6 inhibitors, compared in the Black vs. Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort. Abbreviations: PFS: Progression Free Survival.

Supplementary Files

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