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Racial and ethnic differences in capecitabine toxicity in patients with gastrointestinal tract cancers

Alicia Brazelton[a]*, Soham Yande[a]*, Rita Pope[b], Michael L. Johnson[a], Benjamin Musher[b], Meghana V. Trivedi[a,b]

University of Houston College of Pharmacy; Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX, USA

Abstract

Background Capecitabine is used as a first-line treatment for gastrointestinal (GI) tract cancers. Common toxicities of capecitabine include diarrhea and hand-foot syndrome, which frequently require dose reduction, interruption, or discontinuation. While racial and ethnic differences in capecitabine toxicities have been suggested, they have not been evaluated in a diverse "real-world" setting. We examined differences in capecitabine-related toxicities in different racial and ethnic populations.

Methods The electronic medical records of patients receiving first-line capecitabine-containing regimens for GI malignancies were reviewed. Patients on irinotecan-containing regimens or radiation were excluded because of overlapping toxicities. Multiple logistic regression models were used to test the association between race or ethnicity and capecitabine toxicities while adjusting for other demographic characteristics.

Results One hundred twenty-five patients diagnosed with colon (N=76, 60.8%), rectal (N=22, 17.6%), gastric (N=16, 12.8%), or other GI cancers (N=11, 8.8%) were included. In logistic regression analysis, diarrhea occurrence was significantly lower in the African-American/non-Hispanic (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.08-0.75; P=0.01) compared to Caucasian non-Hispanic population. The occurrence of dose-reduction was significantly higher in the African-American/non-Hispanic population (OR 5.83, 95%CI 1.49-22.80; P=0.01) and in the Caucasian/Hispanic population (OR 4.49, 95%CI 1.09-18.42; P=0.03) compared to Caucasian non-Hispanic population.

Conclusions We have identified racial and ethnic differences in the incidence of capecitabine toxicities, which may help clinicians counsel patients with GI malignancies on capecitabine. There is a need for prospective studies to confirm our findings and to understand the relationship between the incidence of toxicities and dose reductions or discontinuation.

Keywords Capecitabine, ethnicity, hand-foot syndrome, diarrhea, toxicity

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[a]University of Houston College of Pharmacy, Houston, TX, USA (Alicia Brazelton, Soham Yande, Michael Johnson, Meghana V. Trivedi); [b]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX, USA (Rita Pope, Benjamin Musher, Meghana V. Trivedi)

*Co-first author

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Correspondence to: Meghana V. Trivedi, PharmD, PhD, Associate Professor, Department of Pharmacy Practice and Translational Research, University of Houston, Health 2, 4849 Calhoun St., Houston, TX 77204, USA, e-mail: mtrivedi@uh.edu

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Introduction

Capecitabine is an oral prodrug of 5-fluorouracil (5-FU) used as monotherapy, concurrently with radiation, or in combination with other antineoplastic agents for multiple gastrointestinal (GI) tract malignancies, including colorectal, gastroesophageal and pancreatobiliary cancers [1-4]. In contrast to infusional 5-FU, capecitabine obviates the need for an indwelling port and 46-h infusion, but it carries potential toxicities that can be life-threatening if not treated early [4]. The most common side-effects of capecitabine when given at full systemic doses (1000 mg/m^2 b.i.d. for days 1-14 of a 21-day cycle [5]) are diarrhea and hand-foot syndrome (HFS), which presents with redness, swelling, pain, and even desquamation of the palms and soles [5,6]. In fact, as many as 50% of patients on capecitabine monotherapy experience GI toxicity and HFS [7,8], which can be severe enough to warrant dose reductions, delays, and/or discontinuation [1,2]. Severe toxicity occurs in ~15% of patients

treated with capecitabine [9], but to date no biomarkers to predict toxicity have been identified. Being able to risk-stratify patients for capecitabine-related toxicity may help clinicians tailor therapy more reliably and safely.

Previous studies have reported a variable response to cancer treatment based on race and ethnicity [10-16]. Similarly, pharmacogenetic factors may contribute to differences in drug metabolism or clearance and therefore chemotherapy-related toxicities [17,18]. For example, several gene polymorphisms in *DPYD*, the gene encoding the dihydropyrimidine dehydrogenase (DPD) enzyme responsible for degrading 5-FU [19], are associated with an increased risk of severe toxicities with 5-FU-based therapy [20-26]. Recently the European Society of Medical Oncology (ESMO) published guidelines for germline *DPYD* testing prior to starting fluoropyrimidine therapy [27]. Individuals of certain ancestries are more or less likely to carry *DPYD* variants, or to have reduced DPD enzyme activity and a higher risk of 5-FU-related toxicity [28-33]. However, these studies have mostly evaluated bone marrow suppression as a major 5-FU-related toxicity in various populations. While racial and ethnic differences in capecitabine toxicities of diarrhea and HFS have been suggested in case reports [34-37], they have not been systematically evaluated in a diverse, "real-world" population. The purpose of this study was to identify differences in the toxicity profile of capecitabine among patients with different racial and ethnic backgrounds.

Patients and methods

Patients

This study was a retrospective analysis of patients with GI malignancies treated with capecitabine-containing chemotherapy at Ben Taub Hospital, a public hospital serving Harris County's underserved population, between January 2012 and July 2017. This protocol was approved by the Institutional Review Boards at Baylor College of Medicine and the University of Houston.

The study population was patients with early or advanced stages of a GI malignancy undergoing first-line treatment with capecitabine-containing chemotherapy. Patients were excluded if they were undergoing treatment with overlapping toxicities (such as irinotecan or radiation, both of which can cause diarrhea) or if they had insufficient clinical data.

Data collection

Baseline patient demographics and characteristics (race/ethnicity, sex, age at diagnosis, cancer type, and stage at diagnosis) were extracted using the EPIC electronic medical record system at Ben Taub Hospital, Houston, TX, USA. The patients were categorized into the following race/ethnicity categories: Caucasian/non-Hispanic, Caucasian/Hispanic, African American/non-Hispanic, and other. Each adverse event was documented as written by the treating physician in the patient's chart. We also documented dose reductions and discontinuation of therapy due to side-effects. Since the grades of diarrhea and HFS were not documented for all patients, the severity of toxicity could not be documented objectively in many cases.

Statistical analysis

We used descriptive analysis to identify the patient demographics (race/ethnicity, sex, age at diagnosis, and stage at diagnosis) (Table 1). Adjusted logistic regression assessed the association between race/ethnicity and any adverse event, HFS, diarrhea, dose reduction, and discontinuation due to side effects, while controlling for age, sex, and stage at diagnosis.

Results

Baseline characteristics

Of the 769 patients' charts screened, 125 met the eligibility criterion of receiving capecitabine-containing regimens (except those containing irinotecan and radiation) in the first-line setting for the GI malignancy. The majority of patients excluded from the study were on second- or subsequent line therapies. Baseline characteristics are summarized in Table 1. Of these 125 patients, 40 (32%) were Caucasian/Hispanic, 47 (38%) were African American/non-Hispanic, and 38 (30%) were Caucasian/non-Hispanic. Underlying GI malignancies were colon (N=76, 60.8%), rectal (N=22, 17.6%), gastric (N=16, 12.8%), or other (N=11, 8.8%). Within different racial and ethnic groups, there was no significant difference in the proportions of males and females, age at diagnosis, cancer diagnosis, or stage at diagnosis.

Predictors of capecitabine toxicities

African Americans were significantly less likely to have diarrhea (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.08-0.75; P=0.01) than Caucasian/non-Hispanic patients (Table 2). Diarrhea incidence was not different between Caucasian/Hispanics and Caucasian/non-Hispanics. Females (OR 3.85, 95%CI 1.5-8.67; P=0.004) were significantly more likely to have diarrhea than males. There was a trend for a greater risk of HFS in African-American/non-Hispanic (OR 2.26, 95%CI 0.86-5.95; P=0.09), although this result did not reach statistical significance (Table 3). Discontinuation due to side-effects was numerically more common in Caucasian/Hispanic patients (OR 1.97, 95%CI 0.71-5.48; P=0.19) (Table 4) compared to Caucasian/non-Hispanics, but this difference was not statistically significant. Dose reductions due to side-effects were significantly more common in African American/non-Hispanics (OR 5.83, 95%CI 1.49-22.80; P=0.01) and Caucasian/Hispanics (OR 4.49, 95%CI 1.09-18.42; P=0.03) compared to Caucasians/non-Hispanics (Table 5). Dose reductions were

Table 1 Descriptive characteristics stratified by race/ethnicity

Race/Ethnicity	African American/non-Hispanic	Caucasian/Hispanic	Caucasian/non-Hispanic	P-value
Number (%)	47 (37.60)	40 (32)	38 (30.40)	0.58
Sex				
Female	27	15	14	0.08
Male	20	25	24	
Age at diagnosis (years)				
Median (range)	56.55 (37-74)	53.25 (35-80)	55.92 (39-74)	0.19
Diagnosis				
Colon	36	20	20	0.06
Rectal	3	7	12	
Gastric	5	10	1	
Other	3	3	5	
Stage at diagnosis				
1	1	0	0	0.46
2	7	6	5	
3	25	13	17	
4	14	19	16	

Table 2 Factors associated with diarrhea

Parameter	Parameter estimates	Odds ratio (95%CI)	P-value
Age at diagnosis	0.003	1.00 (0.95-1.05)	0.89
Sex			
Female	1.35	3.85 (1.60-9.26)	0.002
Male	ref	ref	
Race/Ethnicity			
African American/ non-Hispanic	-1.34	0.25 (0.08-0.75)	0.01
Caucasian/Hispanic	0.3	1.35 (0.51-3.56)	0.53
Caucasian/ non-Hispanic	ref	ref	
Stage			
Stage 2	0.6	1.83 (0.54-6.11)	0.32
Stage 3	0.54	1.72 (0.69-4.28)	0.23
Stage 4	ref	ref	

CI, confidence interval

Table 3 Factors associated with hand-foot syndrome

Parameter	Parameter estimates	Odds ratio (95%CI)	P-value
Age at diagnosis	-0.00155	0.99 (0.95-1.04)	0.94
Sex			
Female	-0.5	0.6 (0.25-1.44)	0.24
Male	ref	ref	
Race/Ethnicity			
African American/ non-Hispanic	0.81	2.26 (0.86-5.95)	0.09
Caucasian/Hispanic	-0.45	0.63 (0.20-1.95)	0.42
Caucasian/ non-Hispanic	ref	ref	
Stage			
Stage 2	-0.12	0.88 (0.23-3.29)	0.85
Stage 3	0.59	1.81 (0.74-4.40)	0.18
Stage 4	ref	ref	

CI, confidence interval

more common in patients who had HFS (48.65%) compared to those experiencing diarrhea (25.26%).

Discussion

We have identified some racial and ethnic differences in the incidence of capecitabine toxicities and related dose reductions in patients with GI malignancies. We found that African Americans had a lower incidence of diarrhea as compared to non-Hispanic Caucasians. While discontinuation due to side effects trended towards being more common in non-Hispanic Caucasians, dose reductions were significantly more frequent in African Americans and Hispanics compared to non-Hispanic Caucasians. The reasons for these differences could not be assessed in our study.

Our finding of a lower incidence of diarrhea in African Americans compared to non-Hispanic Caucasians is concordant with a previous report of inter-racial differences in diarrhea and other GI toxicities of 5-FU-based chemotherapy [33]. The reason underlying the higher incidence of diarrhea among Caucasians when compared to African Americans is unclear. Germline polymorphisms in genes responsible for 5-FU metabolism could potentially explain interracial differences in the prevalence of capecitabine-induced toxicities. Another explanation could be differential reporting and recording of treatment-related toxicities between different racial groups; this should be evaluated in future studies. Patients on second-line capecitabine and those receiving therapies with overlapping toxicities were excluded to control for the confounding effects of previous and concomitant therapies.

While a prior study found no difference in skin toxicities between African Americans and Caucasians [33],

Table 4 Factors associated with discontinuation due to side-effects

Parameter	Parameter estimates	Odds ratio (95%CI)	P-value
Age at diagnosis	0.02	1.02 (0.97-1.07)	0.32
Sex			
Female	-0.19	0.81 (0.36-1.84)	0.62
Male	ref	ref	
Race/Ethnicity			
African American/ non-Hispanic	0.008	1.00 (0.40-2.54)	0.98
Caucasian/Hispanic	0.68	1.97 (0.71-5.48)	0.19
Caucasian/ non-Hispanic	ref	ref	
Stage	0.28	1.32 (0.39-4.42)	0.64
Stage 2	0.22	1.25 (0.53-2.94)	0.6
Stage 3	ref	ref	
Stage 4			

CI, confidence interval

Table 5 Factors associated with dose-reduction

Parameter	Parameter estimates	Odds ratio (95%CI)	P-value
Age at diagnosis	0.01	1.01 (0.96-1.06)	0.51
Sex			
Female	-0.41	0.65 (0.25-1.68)	0.38
Male	ref	ref	
Race/Ethnicity			
African American/ non-Hispanic	1.76	5.83 (1.49-22.80)	0.01
Caucasian/Hispanic	1.5	4.49 (1.09-18.42)	
Caucasian/ non-Hispanic	ref	ref	0.03
Stage			
Stage 2	0.26	1.30 (0.33-5.12)	0.69
Stage 3	0.57	1.77 (0.66-4.74)	0.25
Stage 4	ref	ref	

CI, confidence interval

our study—which evaluated only HFS, not overall skin toxicities—demonstrated a non-statistically significant (P=0.09) higher incidence of HFS in African American patients (OR 2.26, 95%CI 0.86-5.95). This trend for more frequent HFS in African American patients may explain why they underwent more frequent dose reductions compared to Caucasians. We found that nearly 50% of patients with HFS had dose reductions, compared to only 25% of patients with diarrhea. A possible explanation for this difference is that low-grade diarrhea is often controlled using pharmacological agents and does not require dose reductions, which is not the case with HFS. The twofold rate of HFS among African Americans compared to Caucasians and its contribution to capecitabine dose reductions should be evaluated in future studies.

Our study had several limitations. First, the small sample size may reduce the generalizability of the results and could be a reason why the estimate of risk for HFS did not attain statistical significance at P<0.05. In addition, the retrospective review of the data and capturing toxicities based on clinical notes may have resulted in some misinterpretation. Since erythema may be masked in dark-skinned individuals, a few studies have suggested that the definition of lower grade HFS in African American individuals should be revised to also include hyperpigmentation of palms and soles [35,38]. We also did not evaluate medication adherence and its impact on side-effects in our patients, as the data were not available. However, in the absence of large multi-center clinical trials that include diverse racial and ethnic population, our approach provides a "real-world" assessment of racial and ethnic differences in capecitabine toxicities. Future prospective studies will be necessary to evaluate pharmacogenetic factors contributing to differences in capecitabine toxicities, with documentation of severity of toxicities, time to toxicities, and resulting changes to doses or therapy, in different racial and ethnic minorities.

In summary, the findings of our study can help clinicians manage patients better, in the selection of treatment regimens and anticipation of different toxicities among different racial and ethnic populations. Our study further highlights a need for prospective evaluation of capecitabine toxicities in different racial and ethnic populations and their relationship with dose reductions and discontinuation of therapy.

Summary Box

What is already known:

- Capecitabine is associated with a number of serious side-effects, such as diarrhea and hand-foot syndrome
- Racial and ethnic differences have been suggested as a factor in the occurrence of these capecitabine toxicities
- There is a lack of evidence assessing the association between these toxicities and patients from different racial/ethnic backgrounds

What the new findings are:

- As per our findings, African Americans were less likely to have diarrhea compared to Caucasians/ non-Hispanics
- Dose reductions due to side effects were higher in African Americans/non-Hispanics and Caucasian/ Hispanics compared to Caucasian/non-Hispanic
- Our study also suggests a need for prospective evaluation of capecitabine toxicities in different racial and ethnic populations, and their relationship with dose reductions and discontinuation of therapy

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