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Racial Differences in Clinical Outcomes From Metastatic Breast Cancer: A Pooled Analysis of CALGB 9342 and 9840—Cancer and Leukemia Group B

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Abstract

Purpose—African American women are more likely to be diagnosed with metastatic breast cancer at the time of presentation than whites, and have shorter survival once diagnosed. This study examines racial differences in clinical outcomes in the setting of two large cooperative group randomized clinical trials.

Patients and Methods—The study cohort consisted of 787 white (80%) and 195 African American (20%) patients with metastatic breast cancer enrolled in two successive Cancer and Leukemia Group B (CALGB) trials using taxanes in the metastatic setting. Differences in overall survival (OS), response incidence, and time to treatment failure (TTF) were examined by race. In addition, differences in the incidence of baseline and treatment-related toxicities were examined.

Results—With 779 deaths (166 African Americans and 613 whites), median OS was 14.3 months for African Americans and 18.75 months for whites (hazard ratio [HR] = 1.37; 95% CI, 1.15 to 1.63). When adjusted for prognostic factors, African Americans had a 24% increase in the

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hazard of death compared with whites (HR = 1.24; 95% CI, 1.02 to 1.51). No significant differences in TTF or overall response to therapy were seen. No clinically significant toxicity differences were seen.

Conclusion—African Americans with metastatic breast cancer have an increased hazard of death compared with whites despite the receipt of similar per-protocol treatment, but experience no differences in TTF or overall response to therapy. We hypothesize that more direct and robust measures of comorbidities, and perhaps other factors such as receipt of subsequent therapy could help further explain the observed survival difference.

INTRODUCTION

It is well established that African American women have a lower incidence of but higher mortality rate from breast cancer than whites.^{1,2} Much of this survival disparity has been attributed to more advanced stage at diagnosis.³ Although differences in stage at diagnosis are important in understanding the survival disparity, even when analyses are controlled for stage, African Americans continue to have poorer long-term survival rates. The 5-year relative survival for patients diagnosed with metastatic disease between 1996 and 2002 was 28% for whites and only 16% for African Americans. Of particular concern is that this survival disparity is growing compared with the 1975 to 1979 period, when the 5-year cancer-specific survival was 18% for whites and 15% for African Americans.²

Understanding this stage-specific survival disparity is challenging. Previous researchers have pointed to racial differences in tumor-related factors such as hormone-receptor status and tumor histology.^{3–6} Others have explored the importance of patient-related characteristics such as socioeconomic status and competing comorbidities among African American women.^{3,7–9} Finally, treatment-related factors such as inadequate therapy or higher rates of toxicity, perhaps leading to lower intensity of treatment, have been explored as reasons for the poorer stage-specific survival for African American women.^{10–15}

One way to analyze and isolate the reasons for stage-specific survival differences is to look at outcomes in the setting of a clinical trial. The advantage of analyzing clinical trial data is that eligibility criteria, treatments, and response data are standardized and quantified. Also, information on tumor biology, treatment-related toxicities, and some patient-related characteristics are prospectively collected and can be analyzed to determine whether they have an impact on observed racial differences in survival. This type of analysis has been performed in patients with nonmetastatic breast cancer with several cooperative group studies and demonstrated no differences in breast cancer–specific survival between African Americans and whites after adjusting for demographic and prognostic tumor variables.^{16–18} However, analysis of the Southwest Oncology Group (SWOG) adjuvant breast cancer trials did find that African Americans had lower overall survival (OS) and cancer-specific survival compared with whites even after controlling for demographics and prognostic tumor variables.¹⁹ In the metastatic breast cancer setting, no large cooperative group analysis has been performed. A small study of metastatic breast cancer patients participating in five Piedmont Oncology Association trials found no difference in response rates between African

Americans and whites; however, white patients had a statistically significant 6-month longer median survival.²⁰

The metastatic breast cancer setting offers a unique setting to explore racial differences in survival in that the analysis begins at time when all patients are established to have incurable disease. In this analysis, we examined racial differences in clinical outcomes and the potential reasons behind those differences in the setting of two large cooperative group metastatic breast cancer trials.

PATIENTS AND METHODS

Study Population

The study cohort consisted of patients enrolled in Cancer and Leukemia Group B (CALGB) trials 9342 and 9840. Details of these trials have been reported previously.^{21,22} In brief, between January 15, 1994, and July 31, 1997, CALGB 9342 randomly assigned patients with measurable metastatic breast cancer or inoperable breast cancer and zero to one prior treatments for locally advanced or metastatic disease to three different doses of paclitaxel (175 mg/m², 210 mg/m², or 250 mg/m²) administered over 3 hours every 3 weeks. Between January 15, 1998, and November 14, 2003, CALGB 9840 randomly assigned patients with measurable metastatic breast cancer and zero to one prior chemotherapy regimens for locally advanced or metastatic breast cancer to paclitaxel 175 mg/m² administered every 3 weeks or paclitaxel 100 mg/m² administered weekly. Weekly dose was subsequently amended to 80 mg/m². Patients with HER-2–positive tumors (immunohistochemistry 3+) received trastuzumab; patients with HER-2–negative tumors (immunohistochemistry 0 to 2+) were randomly assigned to receive trastuzumab or not. After excluding 61 patients who were neither white nor African American and 13 patients with unknown ethnicity, the final cohort consisted of 787 white and 194 African American patients.

Statistical Analysis

The primary study end points were tumor response, OS, and time to treatment failure (TTF). OS was calculated as the time from study entry to date last known alive or to date of death resulting from any cause. TTF was measured from study entry to date of first disease progression or to date of death for those patients who died without progression. Patients who were alive and without progression were censored at the date they were last known to be progression free. Tumor response was defined as complete or partial response. Complete response was defined as the disappearance of all lesions. Partial response was defined as a reduction of at least 50% of the sum of the product of all lesions with bidimensional measurements, and with stable or improving nonmeasurable lesions. Patients whose tumors could not be assessed for response because of excessive toxicity or early death were considered nonresponders.

Logistic regression was used to model the relation of tumor response with race and other covariables.²³ Proportional hazards regression was used to model the relation of OS and TTF, respectively, with race and other covariables.²⁴ Each of the two clinical trials whose populations are included herein was stratified by line of therapy. Therefore all models

include indicator variables for line of therapy and for study. For each end point, we constructed two sets of models. The base model included race, study and line of therapy. In addition to the variables in the base model, the full model included other covariables. To assess the relation of race on time to onset of selected toxicity with a severity of at least grade 3, we constructed proportional hazards regression models for each toxicity that had at least a 20% incidence of grade 3 or higher severity. We used the National Cancer Institute Common Toxicity Criteria version 2.0 to grade toxicity.

Covariables of interest were patient demographics (age, menopausal status), clinicopathologic features (tumoral estrogen-receptor [ER] status, number of measurable metastatic sites, performance score, prior adjuvant therapy, pretreatment blood counts) and treatment factors (dose schedule and paclitaxel dose) available at study entry. Race was determined by patient self-report. The following variables were analyzed as dichotomous variables: race (African American *v* white), study (9342 *v* 9840), line of therapy (first *v* second), ER status (negative *v* positive), menopausal status (pre *v* post), prior adjuvant therapy (yes *v* no), and dose schedule (weekly *v* standard). Paclitaxel dose (80, 100, 175, 210, 250), performance score (0 to 3) and patient age were analyzed on a continuous scale. Other variables were transformed, as follows: (1) square root: number of measurable metastatic sites and (2) $\log_{10}$: WBC, platelets and granulocytes.

Main effects were assessed in multivariate regression models using the Wald χ^2 test. Odds ratios (ORs) and hazards ratios (HRs) for main effects and their respective 95% CIs were taken from the corresponding regression model. ORs and their 95% CIs for interaction terms were calculated using the method of Hosmer and Lemeshow.²³

OS, TTF, and time to toxicity distributions were estimated using the Kaplan-Meier product limit technique.²⁴ We used the χ^2 test to compare two proportions and the Mann-Whitney *U* test to compare two groups on continuous variables. Analyses used a modified intention-to-treat approach, including all patients who began protocol therapy regardless of eligibility determination. There was a 5% ineligibility incidence in each racial subgroup.

All *P* values are two sided. We report as significant *P* .05. CALGB statisticians performed statistical analyses on data available in the CALGB database as of February 2005 using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Race in Relation to Other Patient and Disease Characteristics at Study Entry

The study population included 787 white (80%) and 195 African American (20%) patients. Table 1 shows patient and disease characteristics and treatment variables by race and line of therapy. Fifty-one percent of African American patients compared with 41% of white patients were receiving second line therapy for metastatic breast cancer (*P* = .014). Restricting to line of therapy, a larger proportion of African American patients than white patients were younger (first line, *P* < .0001; second line, *P* = .0050) and premenopausal (first line, *P* = .0004; second line, *P* = .033). Additionally, a higher proportion of African American patients had ER-negative tumors (first line, *P* = .0045; second line, *P* = .055). At

study entry African Americans had significantly lower hemoglobin levels (first line, $P = .0001$; second line, $P = .0021$) and significantly higher platelet counts (first line, $P = .0001$; second line, $P = .0057$) than their white counterparts.

Influence of Race on Tumor Response, OS, and TTF

Observed effect: Base models—African American patients had a median OS of 14.3 versus 18.7 months for white patients. African American patients had a median TTF of 4.9 versus 6.4 months for white patients. This translates into a 37% increase in the hazard of death (HR = 1.37; 95% CI, 1.15 to 1.63) for African American patients and a 17% increase in the hazard of failure (HR = 1.17; 95% CI, 0.99 to 1.38) for African American patients over white patients. Tumor response did not differ by race overall (30% v 31%). The results are shown in Table 2. The Kaplan-Meier curves for OS and TTF are shown in Figures 1 and 2.

Adjusted observed effect: Full models—Table 3 shows the observed effect of race on OS and TTF after adjusting for all predictor variables. African American patients continue to have an increased hazard of death compared with whites, albeit of a lower magnitude than seen in the base model (HR = 1.24; 95% CI, 1.02 to 1.51; $P = .030$). The effect of race on TTF remains nonsignificant (HR = 1.11; 95% CI, 0.92 to 1.33; $P = .29$). In addition to race, other variables significantly related to survival were study, line of therapy, ER status, performance score, pretreatment platelet count, and age. Other variables significantly related to TTF were study, performance score, age, ER status, number of metastatic sites at enrollment, and dosing schedule.

Influence of Race on Treatment-Related Toxicities

Table 4 shows the incidence of grade 3+ selected toxicities by race. Compared with white patients, African American patients had a significantly higher incidence of anemia (8% v 3%) and a slightly higher incidence of thrombocytopenia (2% v <1%) and neutropenia (42% v 35%). No differences were seen with respect to grade 3+ leucopenia, lymphocytopenia, infection, or neuropathy.

In total, 20% or more of all patients experienced grade 3 or higher leucopenia, neutropenia, and lymphocytopenia. We assessed the relation of race, after adjusting for study and line of therapy, with time to onset of grade 3+ of each of these three toxicities. Compared with African American patients, white patients had a slightly higher hazard of developing grade 3+ lymphocytopenia (HR = 1.30; 95% CI, 1.00 to 1.69; $P = .048$). Time to onset of grade 3+ leucopenia or neutropenia did not differ by race (data not shown).

DISCUSSION

Consistent with national epidemiologic data, we found that African Americans participating in these two large cooperative group meta-static breast cancer trials have a shorter OS than white patients. We did not, however, see any significant difference in response to therapy or TTF by race. The advantage of clinical trial data is that eligibility and treatment are standardized and several known prognostic tumor and patient-related factors are

prospectively collected and can be accounted for in the analyses. However, even after adjusting for these factors, a persistent survival disparity was seen. The critical question is, why?

Race is a complex variable that is likely acting as a proxy for factors associated with lower socioeconomic status, culture, discrimination, and other factors. In addition the potential that race is also serving as surrogate for underlying differences in tumor and host biology cannot be dismissed. Any time survival differences by race are documented in the presence of what seems to be equal treatment, the issue of potential differences in underlying tumor and patient biology surfaces. Previous studies have documented racial differences in tumor biology such as hormone-receptor status, tumor grade, and S-phase fraction, which may lead to a more aggressive tumor phenotype in African Americans versus whites.^{6,10,25,26} Indeed, a subset analysis of patients enrolled on CALGB 9342 suggests that African American patients were more than twice as likely to have so called triple-negative tumors (ER, progesterone receptor, and HER-2 negative), and that this phenotype was associated with poorer OS.²⁷ Consistent with this observation, recently published work by Carey et al²⁸ suggests that the poorer prognosis basal-like breast tumor phenotype is over-represented in premenopausal African American women. Finally, racial differences in the expression of cell-cycle regulatory proteins,^{29–31} as well as differences in steroid-metabolizing genes, have been noted.^{32,33}

Can differences in tumor biology explain the poorer OS observed in this study? The lack of any significant differences in overall response rates or TTF argues against the predictive importance of racial differences in underlying tumor biology in terms of response to paclitaxel-based therapies. It is, of course, possible that biologic differences that influence survival after disease progression are present, and therefore would not be reflected in lack of TTF or response differences. Also, although the hazard of failure was not statistically significant and diminished in magnitude and significance in the multivariate model, the direction favored an increased hazard of failure for African Americans. Although we feel it is unlikely, we cannot rule out the possibility that a true difference in TTF is present.

In terms of survival, a survival disparity remains even after controlling for measured differences in tumoral ER status. In addition, the interaction between race and tumoral ER status was not of statistical significance for either OS ($P = .27$) or TTF ($P = .47$) suggesting that survival disparities persisted even when only ER-positive or ER-negative patients were considered. Harris et al²⁷ recently published a more detailed analysis of the biologic features of the tumors for some of the patients included in this analysis and their relationship to disease outcome. Although it might have been interesting to examine the effect that these variables had on racial differences in outcome, such a subset analysis would have limited statistical power. However, it is possible that accounting for more detailed tumor biology information such as grade, HER-2 status or gene-expression classifications would have allowed us to explain more of the survival disparity. Of note, in the study by Carey et al, African American women with breast cancer continued to have a poorer OS even after accounting for differences in proportion of women who had ER-negative and basal-like tumors.²⁸

An area that is receiving increased attention is the impact that underlying comorbidities may have in explaining cancer outcome disparities. A recently published study of breast cancer patients suggests that African American patients do have higher rates of comorbidities and that controlling for them could explain 50% of the survival disparity between African Americans and whites.⁸ In the current study, we were able to account for the combined effects of comorbidities and tumor only minimally through an adjustment for performance score. Because there was no significant difference in baseline performance status between African Americans and whites, it is not surprising that this adjustment had little impact on the observed survival disparities. More robust and direct measures of comorbidities may have allowed us to explain more of the survival disparity. Although it is true that patients with debilitating comorbidities would not have been allowed on these trials, little is known about the impact that nonsymptomatic comorbidities such as hypertension, coronary artery disease, and diabetes may have on the survival of metastatic breast cancer patients receiving chemotherapy. This last explanation points to the need to prospectively collect this comorbidity data as part of the clinical trial process.

Additional potentially important prognostic factors such as stage at original diagnosis, year of diagnosis, time from original diagnosis to metastatic disease, socioeconomic status, and the number of additional lines of therapy administered after patients received per-protocol treatment were not incorporated into our models because such information was not reliably available. Although we cannot exclude the possibility that such information may have modified our results, the combination of the available patient and tumor-related information and the standardization of entry criteria, treatment, and follow-up allows for a robust analysis of racial differences in outcomes in the metastatic breast cancer setting. We do believe, however, that more rigorous collection of this type of information should be undertaken in future clinical trial efforts.

Recently, there has been increased focus on the role that toxicity from therapy may play in explaining the poorer OS for African American women with breast cancer. Small studies have suggested that African Americans have higher rates of neutropenia, take longer to complete treatment, receive less intensity of therapy, and are more likely to dropout of therapy perhaps as a result of toxicities.^{12–14} In this study, we examined the issue of toxicity in several ways. First we examined baseline values and, consistent with previous reports, we found borderline differences in granulocytes and lower median hemoglobin levels among African Americans.^{14,34–36} We then examined the highest rates of grade 3+ toxicity by race and found only borderline differences in the incidence of grade 3+ neutropenia and thrombocytopenia, but did find fairly significant differences in the incidence of grade 3+ anemia (hemoglobin < 8.0g/dL). Of note, there was no difference in the hazard of developing grade 3+ neutropenia, which suggests no differences in the degree of therapy-related neutropenia once factors such as study, line of therapy, and time on therapy were controlled for. Finally, we hypothesized that, if there was an association between race and tolerance of therapy that influenced survival or progression, this would be seen with the higher doses of paclitaxel used in the 9342 trial. However, we found no such interaction between race and dose of therapy. In the end, we find no evidence of a clinically meaningful interaction between race and tolerance of therapy that would explain the survival disparity between African Americans and whites reported in this study.

In conclusion, this study demonstrates a 24% increased risk in the hazard of death for African American patients with metastatic breast cancer compared with whites despite standardized eligibility and treatment after adjustments for several tumor, patient, and treatment-related factors. No significant differences in TTF or tumor response were seen. We hypothesize that more direct measures of comorbidities and perhaps other factors such as receipt of subsequent therapy could help further explain the observed differences.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Fig 1. Overall survival by race. Kaplan-Meier analysis of the effect of race on overall survival for patients enrolled in Cancer and Leukemia Group B metastatic breast cancer trials 9342 and 9840. W, white; AA, African American.

Fig 2.

Time to treatment failure by race. Kaplan-Meier analysis of the effect of race on time to treatment failure for patients enrolled in Cancer and Leukemia Group B metastatic breast cancer trials 9342 and 9840. W, white; AA, African American.

Table 1

Patient and Tumor Characteristics by Race and Line of Therapy

Characteristic	First Line				Second Line			
	Patient Race		Patient Race		Patient Race		Patient Race	
	White	African American	White	African American	White	African American	White	African American
	No.	%	No.	%	No.	%	No.	%
All patients	464	100	96	100	323	100	99	100
Study								
9342	78	17	24	25	250	77	81	82
9840	386	83	72	75	73	23	18	18
Age, years*								
< 40	33	7	14	15	20	6	12	12
40–49	100	22	32	33	61	19	19	19
50–59	139	30	31	32	99	31	36	36
60–69	114	25	15	16	100	31	24	24
70+	78	17	4	4	43	13	8	8
Menopausal status								
Premenopausal	84	18	33	34	33	10	18	18
Postmenopausal	380	82	63	66	290	90	81	82
Prior adjuvant therapy								
No	221	48	37	39	143	44	43	43
Yes	236	51	55	57	168	52	53	54
Missing	7	2	4	4	12	4	3	3
Performance score*								
0	222	48	38	40	156	48	45	45
1	209	45	49	51	144	45	43	43
2	22	5	6	6	19	6	8	8
3	1	< 1	2	2	0	0	1	1

Characteristic	First Line					Second Line				
	Patient Race					Patient Race				
	White	African American	No.	%	P	White	African American	No.	%	P
Missing	10	2	1	1		4	1	2	2	
Tumoral estrogen receptor					.0045					.055
Negative	180	39	51	53		117	36	48	48	
Positive	243	52	35	36		170	53	44	44	
Missing	41	9	10	10		36	11	7	7	
No. of measurable sites *					.24					.22
0-1	274	59	54	56		189	59	52	53	
2-3	167	36	35	36		119	37	37	37	
4-6	18	4	7	7		9	3	6	6	
Missing	5	1	0	0		6	2	4	4	
Paclitaxel dose, * mg/m ²					.38					.72
80/100	230	50	47	49		42	13	12	12	
175	185	40	32	33		113	35	38	38	
210	23	5	10	10		83	26	26	26	
250	26	6	7	7		85	26	23	23	
Dose schedule					.91					.82
Weekly	234	50	49	51		281	87	87	88	
Standard	230	50	47	49		42	13	12	12	
Median pretreatment counts										
WBC, k/ μ L *	6.6		6.2		.20	6.1		6.2		.75
Hemoglobin, g/dL *	13.0		11.9		.0001	12.4		11.9		.0021
Platelets, k/ μ L *	264		317		.0001	251		275		.0057
Granulocytes, k/ μ L *	4.4		3.9		.036	4.3		4.1		.58

* Comparison used data on a continuous scale.

Table 2

Observed Effect of Race on Response, OS, and TTF: Base Model

Patient Group	No. of Patients	OS			TTF			Tumor Response		
		Median (months)	HR [*]	95% CI	Median (months)	HR [†]	95% CI	Incidence (%)	OR [‡]	95% CI
All	982		1.37	1.15 to 1.63		1.17	0.99 to 1.38		1.04	0.73 to 1.47
African American	195	14.3			4.9			30		23 to 37
White	787	18.8			6.4			31		28 to 34

NOTE. OR and HR are adjusted for study and line of therapy only.

Abbreviations: OS, overall survival; TTF, time to treatment failure; HR, hazard ratio; OR, odds ratio.

^{*}Ratio of African American:white hazard of death.

[†]Ratio of African American:white hazard of failure.

[‡]Ratio of African American:white odds of response.

Table 3

Observed Effect of All Predictor Variables on OS and TTF

Variable	Comparison for HR (higher v lower)	OS*			TTF [†]		
		P	HR	95% CI for HR	P	HR	95% CI for HR
Race	African American v white	.030	1.24	1.02 to 1.51	.29	1.11	0.92 to 1.33
Study	9342 v 9840	< .0001	1.74	1.33 to 2.28	.0013	1.52	1.18 to 1.96
Line of treatment	Second v first	.0022	1.36	1.12 to 1.65	.14		
Age, years	45 v 65	.044	1.20	1.00 to 1.44	.0041	1.27	1.08 to 1.50
ER status	Negative v positive	< .0001	1.54	1.31 to 1.81	.011	1.21	1.04 to 1.40
Menopausal status		.063			.40		
Performance score	2 v 1	< .0001	1.38	1.21 to 1.58	< .0001	1.29	1.14 to 1.46
Prior adjuvant chemotherapy		.37			.67		
No. of metastatic sites	5 v 3	.61			.028	1.01	1.00 to 1.02
Pretreatment WBC		.58			.84		
Pretreatment platelet count, $\times 10^{-6}$ k/ μ L	325 v 225	.018	1.13	1.02 to 1.25	.16		
Pretreatment granulocytes		.46			.46		
Density	Standard v dense	.076			.0018	1.79	1.24 to 2.58
Dose		.32			.060		

NOTE. HR for OS and TTF are adjusted for all other variables in the model.

Abbreviations: OS, overall survival; TTF, time to treatment failure; HR, hazard ratio; ER, estrogen receptor.

* n = 840, 78% with events.

[†] n = 840 with 89% events.

Table 4

Incidence of Highest Grade of Selected Toxicity Observed During Entire Course of Protocol Therapy (grades 3+)

Group *	Grade 3+		
	No.	%	P
WBC			
White	184	24	.80
African American	42	23	
Platelets			
White	5	< 1	.053
African American	4	2	
Hemoglobin			
White	21	3	.0014
African American	14	8	
Granulocytes			
White	267	35	.080
African American	76	42	
Lymphocytes			
White	302	39	.82
African American	70	38	
Infection			
White	41	5	.22
African American	14	8	
Sensory neuropathy			
White	140	18	.89
African American	34	19	
Motor neuropathy			
White	60	8	.95
African American	14	8	

* White patients, n = 767; African American patients, n = 182.