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Race, age and gender-based characteristics and toxicities of targeted therapies on phase I trials

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Abstract

Background—The impact of age, gender and race-based differences on safety and efficacy in phase I clinical trials has not been well studied.

Methods—We analyzed data from phase I clinical trials evaluating targeted biologic agents in patients with advanced solid malignancies. Race and gender distribution of enrolled patients was compared to the referral population demographics at the city, metro and state level. Association between age, gender and race with type, frequency and severity of treatment-emergent toxicities and clinical benefit was assessed using univariate and multivariable models.

Results—Data from 117 eligible patients: Blacks/Caucasians/Others (27/85/5); male/female (66/51). Blacks were younger than Caucasian patients (median age of 56 vs. 62 years, $p=0.004$). Nausea/vomiting was more frequent in female patients (43% vs. 24%, $p=0.03$) while hematologic toxicity was more likely in Whites. While median time on treatment was comparable (113 vs. 91; $p=0.840$) the median overall survival was significantly shorter for Blacks versus Caucasians (7.4 vs. 11.4 months; $p=0.0227$). Black race (HR: 2.11; 95%CI: 1.24–3.60; $p=0.006$) and older age (HR: 1.03; 95% CI: 1.00–1.06; $p=0.029$) were associated with increased risk of death.

Conclusions—Age-, gender- and race-based disparities were observed with specific toxicity and survival outcomes on phase I clinical trials of anticancer agents.

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Keywords

Phase I study; targeted therapy; tolerability; toxicity; race; gender

1. Background

Cancer is the second leading cause of death in the United States. Worldwide, approximately 14.1 million new cancer cases and 8.2 million deaths were estimated in 2012.[1] There were 1,685,210 new cancer cases and 595,690 cancer-related deaths in the US in 2016.[2] Once diagnosed with cancer, the outcome for patients differs significantly by race and ethnicity. Compared with Whites, US Blacks have poorer 5-year relative survival for nearly all cancer types. Minority males have a greater probability of dying from cancer within 5 years of diagnosis than Whites, and Black women have the lowest 5-year cancer-specific survival (56.0%) of all female cancer patient subgroups.[3]

The astounding successes witnessed in the last decade with targeted small molecule anticancer therapies were made possible by improved understanding of tumor biology leading to the development of rationally designed drugs to exploit specific vulnerabilities in the cancer cell. Leading examples include erlotinib, gefitinib, crizotinib, ceritinib and osimertinib in lung cancer;[4–7] imatinib, nilotinib, and dasatinib for chronic myeloid leukemia;[8, 9] everolimus and palbociclib in breast cancer[10] and abiraterone in prostate cancer.[11] Clinical trials that established the efficacy of these agents typically progress in sequence starting with the phase I safety and dose defining clinical trial, which set the stage for efficacy testing in phase II and phase III settings.

Willingness to participate in clinical trials is comparable between US minorities and non-Hispanic Whites.[12, 13] However, there is continuing challenge with adequate representation of minority and older patients in cancer clinical trials despite policy prescriptions.[14–16] A comprehensive analysis of cancer therapeutic trials sponsored by the National Cancer Institute (NCI) of the NIH conducted 10 years after the promulgation of the NIH Revitalization Act revealed that racial/ethnic minorities continued to be underrepresented in clinical trials.[17–19] A similar review of 86 randomized clinical studies published in leading medical journals showed continued underrepresentation of women and minorities in clinical trials.[19] An analysis of all NCI-sponsored trials 20 years after the NIH Revitalization Act showed that non-White participants constitute less than 5 percent of trial participants.[20]

The phase I clinical trial establishes appropriate doses for new drugs and thus serves as the bedrock of therapeutic innovation in cancer care. A lack of diversity and failure to adequately include minority and older patients during this phase of drug development has a high likelihood to perpetuate outcome disparity if the established doses for regulatory approval turn out to be intolerable or of suboptimal efficacy for minority patients. There are gender-based differences with a 1.5 to 1.7-fold greater risk of adverse drug reaction in females.[21, 22] Similarly, significant race-based variations occur in drug metabolizing enzymes such as the cytochrome P450 family of enzymes which can result in unexpected toxicity.[22, 23]

Very little is known through published literature regarding possible gender, age and race-based differences in toxicity and efficacy signal on phase I trials of anticancer agents. We therefore reviewed our institutional experience on phase I clinical trials of targeted agents to elucidate potential disparities between patient subgroups defined by age, gender and race.

2. Methods

2.1 Patients an study selection

Patients with advanced cancers enrolled on investigator-initiated phase I clinical trials conducted at the Winship Cancer Institute of Emory University between 2010 and November 2013 were eligible. Phase I studies sponsored by Emory investigators that enrolled patients with advanced solid malignancies without limitation on age, gender and ethnic or racial background were eligible. Demographic data was abstracted from electronic medical record while trial-specific data were collected from the electronic database for the selected studies. We employed data from patients enrolled on five different investigator-initiated phase I clinical trials conducted at our center. The selected studies evaluated one or more targeted agents including: mTOR inhibitor everolimus with docetaxel (NCT00406276); HSP90 inhibitor, ganetespib, with docetaxel (NCT01183364); everolimus and lenalidomide (NCT01218555); axitinib with temsirolimus (NCT01529138) and bortezomib plus sunitinib (NCT00720148). The Emory University Institutional Review Board approved this study.

2.2 Toxicity and efficacy assessment

Patients were treated in accordance with the protocol of the trial on which they were enrolled. Toxicity assessment on all studies was performed according to NCI CTCAE v. 4.0 criteria. Efficacy assessments performed according to the protocol-specified schedule using cross sectional imaging according to RECIST 1.0 guidelines. Efficacy was also measured as length of time on treatment and overall survival (OS).

2.3 Statistical analysis

Patient and tumor characteristics were summarized as frequency (percentage, %) for categorical variables and mean ($\pm$ standard deviation) or median (range) for continuous variables. PFS and OS were estimated by the Kaplan-Meier method and the log-rank test was used to assess the difference in PFS and OS stratified by race and gender. Race and gender distributions of enrolled patients were compared to the referral population using 2010 census data for the city, metro and entire state by chi-square test. We compared Black and Caucasian patients with respect to demographics, type, grade and number of toxicities, dose limiting toxicities (DLT) and dose levels at which patients were treated using analysis of variance, Wilcoxon rank-sum test, and chi-square test as appropriate. Univariate and multivariable analyses were employed to assess whether clinical and demographic characteristics (age, gender, race, weight and BMI) predict DLT, clinical benefit and survival using a logistic regression, negative binomial regression, and Cox proportional hazards regression models, respectively.[24] The proportional hazards assumption was evaluated with Schoenfeld residuals and a Kolmogorov-type supremum test.[25] Multivariable analyses were performed by including gender, race, age, and body weight in a model and a

backward variable selection method with an alpha level of 0.1 for removal criteria. All analyses were conducted using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina) and statistical significance level was set at < 0.05 .

3. Results

3.1 Studies

Four of the five studies selected for this analysis have completed enrollment with final results published for two studies.[26, 27]

3.2 Patients and tumor characteristics

There were 121 eligible patients treated on the five selected phase I studies. Of these, 117 patients evaluable for toxicity were included in these analyses, 51 (44%) females and 66 (56%) males. The mean age was 60.5 (± 9.83) years and self-identified race was Black in 27 (23%), White in 85 (73%) and other racial groups in 5 (4%) patients. Using the 2010 census data as reference, there was underrepresentation of minority patients on the selected phase I studies in comparison to the racial/ethnic distribution of the city of Atlanta, the Atlanta metro area (DeKalb, Fulton, Gwinnett, Clayton, and Cobb counties) and the state of Georgia (Table 1). The overall gender distribution of the clinical trial participants did not significantly differ from the catchment area population (Table 1). Tumor histologies included 36 cases of lung cancer (26%), 15 (11%) colorectal cancers, 14 (10%) head and neck cancers, 12 (9%) thyroid cancers, 10 (7%) pancreatic cancers, 10 (7%) salivary gland tumors, 8 (6%) kidney cancers, and 31 (23%) patients with other histologies.

3.3 Adverse events and dose limiting toxicities

There was no significant difference between Black and Caucasian participants with respect to overall grade of toxicity, type of toxicity, number of toxicities (Table 2) and whether the toxicity was a DLT (Table 3). There was a significant difference in age with Black participants being younger than Caucasians (55.8 vs. 62.0 years; $p = 0.004$; Table 3). Univariate analysis revealed significant differences in types of toxicities by race and gender. Whites were more likely to experience hematologic toxicity than Blacks (67.1% vs. 48.2%; $p = 0.077$; Table 3) while female patients were more likely to experience symptoms of nausea and vomiting (43.4% vs. 24.24%; $p = 0.03$; Table 3). There was no association between DLT experience and patient characteristics on univariate and multivariate analyses although there was a trend for increased DLT in Whites (Table 4A).

3.4. Clinical Benefit

We employed duration on treatment and the OS as read outs of clinical benefit. The median (range) duration on study was 2.89 months (0.23–32.86) and was comparable between Blacks and Caucasians (3.72 vs. 2.99 months; $p = 0.840$; Table 2). Age and body weight showed significant correlation with duration on study by univariate and multivariable analyses, while race and gender showed no significant association (Table 4B). Univariate analysis showed a significant association between race and OS, with Blacks having a higher risk of death than Caucasians (HR: 1.81; 95% CI: 1.08–3.04; $p = 0.025$; Figure 1 and Table 4C), which remained significant on multivariate analysis (HR: 2.11; 95% CI: 1.24–3.60;

p=0.006; Table 4C. Older age was also associated with a higher risk of death (HR: 1.03; 95% CI: 1.00–1.06; p=0.029; Table 4C) but no significant difference by gender (Figure 1).

4. Discussion

Differences in safety across race, gender and age subgroups remain an understudied aspect of phase I clinical trials despite many prior studies focusing on predictors of toxicity and participants' experience on cancer clinical trials.[28, 29] Performance status and type of investigational agents were previously identified as predictors of toxicity on phase I trials. [30] Whether gender, race or age could be associated with the type and severity of toxicities on phase I studies remains to be explored.[30] A review of 460 phase I clinical trials conducted by the Cancer Therapy Evaluation Program of the NCI enrolling 11,935 participants showed meaningful clinical benefit with objective response in 10.6% of participants together with a low mortality rate of 0.49%.[31] A more recent analysis of the same CTEP database using contemporary data from 1908 patients enrolled between 2000 and 2009 showed a higher probability of response and better survival for patients treated at higher doses of investigational agents (odds ratio for increased response = 1.56, p = 0.10; hazard ratio for death = 0.37, p = 0.008).[32] These studies, however, failed to explore the potential contribution of participants' racial background to the results of these studies. The current study therefore represents a systematic attempt to uncover whether potential disparities exist in clinical benefits and treatment-emergent toxicities in patients on phase I clinical trials.

Low enrolment of US cancer patients of minority racial background has been well described in the literature. We noted a 24% enrollment rate for Blacks on the selected phase I trials included in this analysis. This rate is significantly higher than that previously reported for US minority participation in clinical trials and in part reflects the diversity of our catchment area population where Blacks make up 58%, 44% and 34% of the City, Metro and State population, respectively. Of note, there are no significant differences in age-adjusted cancer incidence rates of 395, 431, 562 and 513 per 100,000 individuals for Black female, White female, Black male and White male, respectively, in our catchment population.[33] Nonetheless, the 24% rate of enrolment of Blacks is much more reflective of the overall state demographics perhaps because our phase I program is the only such dedicated program for the state. Overall, strategic placement of phase I and other cancer clinical trials at institutions serving a diverse patient population could therefore be an effective strategy to improve the enrolment of US minority patients in cancer clinical trials.

The primary objective of phase I studies is the establishment of a safe dose to be carried forward into future efficacy testing. Due to the low enrollment of minority patients in cancer trials, there is a valid concern that the dose determined from these studies may not be representative of the tolerability or potential efficacy of the agent in the minority patient population. Reassuringly, we observed no significant differences between Blacks and Caucasians in terms of frequency and degree of toxicities experienced while on study. Caucasian patients were more likely to experience a DLT despite comparable distribution of Whites and Blacks across various dose cohorts. The observed trend of a lower rate of hematological toxicities in Blacks compared to Whites may be a contributory factor since

DLT were defined mostly by hematological toxicities in the studies selected for this analysis. Consistent with prior reports, there was a significant association of female gender with higher likelihood of gastrointestinal toxicities, specifically, nausea and vomiting.[34–36] The gender and race-based differences observed in our phase I trial participants highlight the need to ensure diversity at the earliest stages of clinical development of anticancer agents. Indeed, 30% of toxicities encountered in late stage studies were not observed in the phase I studies and there was a significant discordance between doses established in phase I studies and the final approved dose of the drug following registration studies.[37]

The median time on treatment of 88 days observed in our population is comparable to other phase I studies in unselected treatment refractory patients.[38–40] There was no significant difference between Caucasians and Blacks in terms of time on treatment. The median OS for Blacks (7.1 months) and Whites (11.1 months) was generally comparable to that reported for patients treated on phase I trials from other institutions.[30, 39–43] Nonetheless, there was a disparity in OS in our patient population with a 2-fold higher risk of death in Blacks compared to Whites (HR: 2.037; 95%CI: 1.182–3.512, $p=0.01$). This survival difference is consistent with other reports suggesting a worse outcome for US cancer patients of minority race. This has been ascribed in major part to challenges with access to care. This retrospective analysis is unable to accurately clarify the reason for this disparity. Treatment at higher doses of investigational agents on phase I study is associated with greater likelihood of clinical benefit[32] but the proportion of Blacks and Whites treated at higher doses on the selected studies was not significantly different. Differences in other interventions that patients received after coming off the phase I study could be partly responsible but we do not have post-study treatment data for these patients. Paradoxically, differences in access to high quality end of life palliative care and avoidance of futile aggressive therapies that may hasten patient demise may be a contributory factor since US patients of minority race are more likely to pursue aggressive end of life care with detrimental outcome.[44–48]

Important limitations to be noted with respect to our study include the relatively small overall sample size, which may not be sufficient to uncover unique but rare toxicities that may disproportionately affect patient subgroups. We pooled trials conducted at a single institution with predominantly Whites and Blacks, which limits the generalizability of our findings to other US minority populations such as Asians and Hispanics. Nonetheless, our report remains the only study of its type with sufficient number of minority patients enrolled on phase I trials to allow a systematic comparison. Also, we focused primarily on patients receiving targeted agents. Since cytotoxic agents remain the bedrock of cancer treatment, the comparable outcome in safety and benefit between Blacks and Whites treated on phase I studies of targeted agents may not be the same with cytotoxic agents. In conclusion, this systematic study of potential disparities in adverse events and clinical benefit in patients enrolled on phase I studies of anticancer agents has reassuring findings overall, while also highlighting unique differences with respect to race and gender that should be carefully addressed in the design and conduct of phase I studies of anticancer agents.

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Figure 1.

A. Kaplan-Meier curves for ethnicity on OS showing improved survival for Whites over Blacks both in terms of median OS (0.94 vs. 0.62 years; $p=0.0227$) and the estimated 2- year survival rates (41.17% vs. 17.79%). The disparity in survival was most pronounced after 6 months, which is beyond the median time on study suggesting that other factors beyond treatment received on the phase I trial may be at play.

B. Kaplan-Meier curves for gender on OS showing no significant difference between females and males in OS (0.92 vs. 0.83 years; $p=0.5339$) or estimated 2-year survival rates (33.6% vs. 34.4%).

Table 1

Ethnicity and Gender Disparities between State of Georgia, City of Atlanta, Metro Atlanta, and Emory Patients

Population	Ethnicity		P-value *
	Black	Caucasian	
Emory	27 (24.11)	85 (75.89)	< 0.001
Atlanta	226,802 (58.44)	161,281 (41.56)	
Emory	27 (24.11)	85 (75.89)	< 0.001
Metro Atlanta †	1,347,800 (44.29)	1,695,374 (55.71)	
Emory	27 (24.11)	85 (75.89)	0.030
Georgia	2,954,734 (33.81)	5,783,529 (66.19)	

Population	Gender		P-value *
	Male	Female	
Emory	66 (56.41)	51 (43.59)	0.150
Atlanta	208,968 (49.75)	211,035 (50.25)	
Emory	66 (56.41)	51 (43.59)	0.090
Metro Atlanta †	1,635,029 (48.58)	1,730,268 (51.42)	
Emory	66 (56.41)	51 (43.59)	0.100
Georgia	4,729,171 (48.82)	4,958,482 (51.18)	

Data are presented as number of patients (%).

* P-value is calculated by chi-square test.

† Metro Atlanta includes DeKalb, Fulton, Gwinnett, Clayton, and Cobb counties.

Table 2

Univariate Association of Ethnicity with Covariates

Variable	All patients (N=117)	Ethnicity		P-value*
		Black (N=27)	Caucasian (N=85)	
Worst grade				0.478
1	21 (17.95)	5 (18.52)	16 (18.82)	
2	32 (27.35)	7 (25.93)	22 (25.88)	
3	39 (33.33)	12 (44.44)	27 (31.76)	
4	25 (21.37)	3 (11.11)	20 (23.53)	
DLT				
Yes	41 (35.04)	7 (25.93)	32 (37.65)	0.265
No	76 (64.96)	20 (74.07)	53 (62.35)	
Gender				
Female	51 (43.59)	12 (44.44)	37 (43.53)	0.933
Male	66 (56.41)	15 (55.56)	48 (56.47)	
Age	60.5 ($\pm$ 9.83)	55.78 ($\pm$ 10.72)	62.02 ($\pm$ 9.31)	0.004
Number of toxicities	7 (1 – 32)	5 (1 – 27)	7 (1 – 32)	0.281
BMI	26.3 (18.7 – 54.2)	26.7 (20.1 – 43.2)	26.1 (18.7 – 54.2)	0.467
Weight (kg)	78.4 (48 – 163.4)	43.2 78.4 (48 – 117.3)	54.2 79 (48.4 – 163.4)	0.927
Duration on Study (Months)	2.89 (0.23 – 32.86)	117.3 3.72 (0.46 – 10.76)	2.99 (0.36 – 32.86)	0.840

Data are presented as number of patients (%), mean ($\pm$ SD) or median (range).

Abbreviation: DLT, dose limiting toxicity; BMI, body mass index.

* P-value is calculated by ANOVA for age; Wilcoxon rank-sum test for number of toxicity, BMI, weight, and duration on study; chi-square test for worst grade, DLT, and gender.

Table 3

Univariate Association of Ethnicity and Gender with Toxicities

	Ethnicity		
Variable	Black (N=27)	Caucasian (N=85)	P-value [*]
Hematologic toxicity			
Yes	13 (48.15)	57 (67.06)	0.077
No	14 (51.85)	28 (32.94)	
Liver toxicity			
Yes	5 (18.52)	18 (21.18)	0.766
No	22 (81.48)	67 (78.82)	
Nausea/Vomiting			
Yes	10 (37.04)	27 (31.76)	0.612
No	17 (62.96)	58 (68.24)	
Dose level treated			
1	3 (15)	12 (16.9)	0.220
2	10 (50)	21 (29.58)	
> 2	7 (35)	38 (53.52)	

	Gender		
Variable	Male (N=66)	Female (N=51)	P-value [*]
Hematologic toxicity			
Yes	43 (65.15)	31 (60.78)	0.627
No	23 (34.85)	20 (39.22)	
Liver toxicity			
Yes	14 (21.21)	10 (19.61)	0.831
No	52 (78.79)	41 (80.39)	
Nausea/Vomiting			
Yes	16 (24.24)	22 (43.14)	0.030
No	50 (75.76)	29 (56.86)	
Dose level treated			
1	9 (16.36)	8 (20)	0.899
2	19 (34.55)	13 (32.5)	
> 2	27 (49.09)	19 (47.5)	

Data are presented as number of patients (%).

* P-value is calculated by chi-square test.

Table 4**A Univariate and Multivariable Analysis for Predictors of DLT**

Variable	Univariate		Multivariable *	
	N	P-value	Odds Ratio (95% CI)	P-value
Gender, Female versus Male	51 vs. 66	1.38 (0.64–2.97)	0.406	1.35 (0.56–3.25) 0.509
Race, Black versus Caucasian	27 vs. 85	0.58 (0.22–1.52)	0.269	0.62 (0.23–1.70) 0.354
Age	117	1.02 (0.98–1.06)	0.321	1.01 (0.97–1.06) 0.535
BMI	117	0.99 (0.93–1.05)	0.693	Not included
Weight (kg)	117	1.00 (0.98–1.02)	0.730	1.00 (0.98–1.02) 0.930

B Univariate and Multivariable Analyses of Duration on Study (Days)

Variable	Univariate		Multivariable	
	N	P-value	Rate Ratio (95% CI)	P-value
Gender, Female versus Male	51 vs. 64	1.15 (0.83–1.59)	0.409	†
Race, Black versus Caucasian	27 vs. 83	0.78 (0.53–1.13)	0.193	†
Age	115	0.99 (0.97–1.00)	0.099	0.99 (0.97–1.00) 0.093
BMI	115	1.02 (0.99–1.04)	0.225	Not included
Weight (kg)	115	1.01 (1.00–1.02)	0.028	1.01 (1.00–1.02) 0.029

C Univariate and Multivariable Overall Survival Analyses

Variable	Univariate		Multivariable	
	N	P-value	Hazard Ratio (95% CI)	P-value
Gender, Female versus Male	50 vs. 66	0.86 (0.54–1.37)	0.534	†
Race, Black versus Caucasian	26 vs. 85	1.81 (1.08–3.04)	0.025	2.11 (1.24–3.60) 0.006

C Univariate and Multivariable Overall Survival Analyses

Variable	Univariate		Multivariable	
	N	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)
Age	116	1.02 (0.99–1.04)	0.117	1.03 (1.00–1.06)
BMI	116	0.97 (0.93–1.01)	0.129	Not included
Weight (kg)	116	0.99 (0.98–1.00)	0.076	[‡]

Abbreviation: DLT, dose limiting toxicity.

112 observations were used in the multivariable logistic regression model.

*None of the variables is significant at alpha level of 0.1.

Abbreviation: DLT, dose limiting toxicity.

110 observations were used in the multivariable negative binomial model.

[‡]Dropped out of the model.

Abbreviation: DLT, dose limiting toxicity.

111 observations were used in the multivariable Cox proportional hazards model.

[‡]Dropped out of the model.