REGULAR ARTICLE

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The impact of race, ethnicity, and obesity on CAR T-cell therapy outcomes

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Key Points

- Race, ethnicity, and BMI did not impact CAR T-cell efficacy or neurotoxicity outcomes.
- Hispanic patients were more likely to experience severe cytokine release syndrome following CAR T-cell therapy.

Cancer outcomes with chemotherapy are inferior in patients of minority racial/ethnic groups and those with obesity. Chimeric antigen receptor (CAR) T-cell therapy has transformed outcomes for relapsed/refractory hematologic malignancies, but whether its benefits extend commensurately to racial/ethnic minorities and patients with obesity is poorly understood. With a primary focus on patients with B-cell acute lymphoblastic leukemia (B-ALL), we retrospectively evaluated the impact of demographics and obesity on CAR T-cell therapy outcomes in adult and pediatric patients with hematologic malignancies treated with CAR T-cell therapy across 5 phase 1 clinical trials at the National Cancer Institute from 2012 to 2021. Among 139 B-ALL CAR T-cell infusions, 28.8% of patients were Hispanic, 3.6% were Black, and 29.5% were overweight/obese. No significant associations were found between race, ethnicity, or body mass index (BMI) and complete remission rates, neurotoxicity, or overall survival. Hispanic patients were more likely to experience severe cytokine release syndrome compared with White non-Hispanic patients even after adjusting for leukemia disease burden and age (odds ratio, 4.5; P = .001). A descriptive analysis of patients with multiple myeloma (n = 24) and non-Hodgkin lymphoma (n = 23) displayed a similar pattern to the B-ALL cohort. Our findings suggest CAR T-cell therapy may provide substantial benefit across a range of demographics characteristics, including for those populations who are at higher risk for chemotherapy resistance and relapse. However, toxicity profiles may vary. Therefore, efforts to improve access to CAR therapy for underrepresented populations and elucidate mechanisms of differential toxicity among demographic groups should be prioritized.

Introduction

Over the past decade, chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment landscape for multiply relapsed or chemotherapy-refractory hematologic malignancies.[1] As a testament

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to this success, there are currently 6 unique Food and Drug Administration–approved CAR T-cell constructs available for use in relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL),[2] B-cell non-Hodgkin lymphoma (NHL),[3,4] and multiple myeloma (MM).[5,6] Despite the success of CAR T-cell therapy, whether its considerable benefits extend commensurately to high-risk demographic subgroups such as racial/ethnic minorities and patients with obesity is poorly understood. The poor representation of racial and ethnic minorities in early-phase and pivotal CAR T-cell trials has limited this analysis.[7,8]

Cancer outcomes, particularly with conventional therapies, are worse in certain racial/ethnic minority populations and those with obesity. Hispanic patients with B-ALL experience higher mortality,[9] greater toxicity, and more chemotherapy complications than non-Hispanic patients.[10,11] Black race[12] and Hispanic ethnicity are independent adverse prognostic factors for B-ALL survival.[13] High-risk cytogenetics (eg, IgH-CRLF2 and IKZF1) conferring chemotherapeutic resistance are disproportionally found in Hispanic patients with B-ALL.[14] In adults with NHL, analysis of the Surveillance, Epidemiologic, and End Results database from 1997 to 2015 demonstrated that Black patients experience worse survival outcomes compared with White patients despite decreasing incidence of disease overall.[15] Among patients diagnosed with MM, Black patients have worse survival outcomes compared with White patients even after controlling for receipt of triplet induction therapy and autologous stem cell transplant.[16]

Another risk factor impacting cancer outcomes is obesity. Childhood obesity is associated with increased risk of developing B-ALL, relapsing, and having chemotherapy-resistant disease.[17,18] Patients with B-ALL and obesity also have a higher prevalence of high-risk cytogenetics such as CRLF2 rearrangements,[19] which is further amplified among Hispanic patients.[17] Moreover, obesity independently predicts lower event-free survival rates in pediatric B-ALL.[20] In adults, obesity has been shown to increase the risk of developing MM[21] and independently increase mortality risk in patients with NHL.[22]

Whether similar disparities in outcome for racial/ethnic minorities and patients with obesity extend to immunotherapy is less well understood. Some studies support a more favorable response in adult patients with obesity receiving immunotherapy,[23,24] particularly with checkpoint inhibitor therapy,[25] but data on adoptive cell therapy are limited.[20,26] A recent study demonstrated an association between visceral adiposity and higher body mass index (BMI) with severe cytokine release syndrome (CRS) following CD19 CAR T-cell therapy.[27] Given the ability of CAR T cells to overcome chemotherapy resistance, which minority and obese populations may be particularly at risk for, we hypothesized that clinical responses may be similar across race and ethnicity and sought to explore the intersection with obesity. Accordingly, we evaluated the impact of race, ethnicity, and obesity on CAR T-cell therapy efficacy and toxicity outcomes across 5 early-phase clinical trials encompassing 4 distinct CAR constructs and 3 hematologic malignancies in pediatric and adult patients.

Methods

Study design

This retrospective study included 5 phase 1 CAR T-cell trials at the National Cancer Institute (NCI). All patients had B-cell malignancies, including B-ALL, NHL, and MM, treated with CAR T-cell therapy between 2012 and 2021. CAR constructs included CD19, CD22, CD19/22 bispecific, and B-cell maturation antigen (BCMA). The CD19 and BCMA CAR constructs used a CD28 costimulatory domain, whereas the CD22 and CD19/22 bispecific CAR constructs had a 4-1BB domain. All individual protocols were approved by the NCI Institutional Review Board, including the retrospective study for this analysis, which is registered at www.clinicaltrials.gov as #NCT03827343. The study was conducted according to the Declaration of Helsinki.

Patient demographics, including sex, race, ethnicity, and pretreatment characteristics, such as BMI and disease burden, were verified by study investigators and collected for analysis from the electronic medical record. Home ZIP codes were used to assess geographic referral patterns as our center is a quaternary and federally funded institution and receives patient referrals from across the world. Race and ethnicity were classified into 3 categories: White non-Hispanic, Hispanic, and all other non-Hispanic. Obesity, overweight, normal weight, and underweight were defined as BMI $\geq$ 30, 25 to <30, 18.5 to <25, and <18.5 kg/m^2, respectively, in adults aged $\geq$20 and as BMI $\geq$ 95th, 85th to <95th, 5th to <85th, and <5th percentiles, respectively, in pediatric patients aged 2 to <20 per Centers for Disease Control and Prevention guidelines. BMI was calculated prior to lymphodepleting chemotherapy for all patients. Baseline disease burden in the bone marrow for patients with B-ALL was defined as M1 (<5% blasts), M2 (5% to 25%), and M3 (>25%), with all patients required to have detectable disease at infusion.

Outcomes of interest

The primary objective was interrogating the association of race/ethnicity and BMI with CAR T-cell therapy efficacy and toxicity in patients with B-ALL. Efficacy was measured by the complete remission (CR) rate. In B-ALL, CR was defined as negative measurable residual disease (<0.01% blasts) in the bone marrow 28 days after CAR T-cell infusion. Toxicity outcomes were evaluated by maximum severity of CRS, as graded by the American Society for Transplantation and Cellular Therapy (ASTCT) consensus guidelines,[28] and neurotoxicity, recorded by its presence or absence given our inability to reconcile grading criteria across the treatment period with more recent ASTCT guidelines. Secondary objectives included evaluation of representation across demographic subgroups, examining geographic referral patterns, and identifying the association of race/ethnicity and BMI with overall survival in patients with B-ALL treated with CAR T-cell therapy. Because of the small number of patients with NHL or MM, CAR T-cell efficacy and toxicity were descriptively analyzed for these groups. In NHL and MM, CR was defined per the Cheson criteria[29] and International Myeloma Working Group Uniform Response Criteria,[30] respectively.

Statistical analysis

Patient, disease, and treatment characteristics were summarized with descriptive statistics. Univariate logistic regression was employed to evaluate the association of demographic factors with efficacy and toxicity outcomes. Age was treated as a continuous variable and also dichotomized as adult (age $\geq$18) vs pediatric (age <18). All outcomes were dichotomized as present vs absent (CR, neurotoxicity) and grade 3 to 5 vs grade 0 to 2 (CRS). For select

outcomes, multivariable logistic regression models were generated incorporating parameters using backward selection (retention criteria, $P < .05$). The number of variables in the final model was limited to prevent overfitting per number of outcome events. Survival was calculated using the Kaplan-Meier method from date of last CAR T-cell infusion to date of death or last follow-up with censor date of August 9, 2021. All statistics were performed in Prism (GraphPad) and SAS Version 9.4.

Results

Patient characteristics and demographics (all subjects)

Our analysis included a total of 186 unique infusions of CAR T-cell therapy over the study period. This included 139 (74.7%) infusions for B-ALL (used for primary analysis), 23 (12.4%) infusions for NHL, and 24 (12.9%) infusions for MM. Reinfusion strategies were excluded from this analysis. Eleven patients received 2 different products at 2 different timepoints. These infusions were considered independent, as interim treatment, disease characteristics, and apheresis materials differed between the 2 infusions (supplemental Table 1). Geographically, 120 (64.5%) patients were referred from within the United States, encompassing 32 states and the District of Columbia (Figure 1A); the remaining 55 (35.5%) patients originated from outside the United States (Figure 1B).

Cohort with acute lymphoblastic leukemia (n = 139 infusions)

Patient characteristics and demographics. Among 139 patients infused for B-ALL, median age was 15.1 years (interquartile range [IQR], 9.6-21.2), and 98 (70.5%) patients were male. This cohort included a total of 40 (28.8%) Hispanic patients and 5 (3.6%) Black patients. With respect to BMI, 41 (29.5%) patients were overweight or obese (Table 1). Age and BMI showed a moderate positive correlation (supplemental Figure 1). Median age and sex distribution were similar in non-Hispanic patients compared with Hispanic patients. Although a higher percentage of Hispanic patients were obese (22.5%) compared with non-Hispanic patients (12.1%), the percentage of Hispanic patients classified as overweight or obese (32.5%) was similar to non-Hispanic patients (28.3%) (Table 2).

Table 1. Patient characteristics

	B-ALL (n = 139)	MM (n = 24)	NHL (n = 23)
Median age, y (IQR)	15.10 (9.55, 21.20)	54.50 (52.75, 59.25)	54.00 (45.50, 64.00)
Male (%)	98 (70.5)	12 (50.0)	13 (56.5)
Race/ethnicity (%)			
White (non-Hispanic)	77 (55.4)	17 (70.8)	19 (82.6)
Hispanic	40 (28.8)	3 (12.5)	2 (8.7)
Asian	14 (10.1)	0 (0.0)	1 (4.3)
Black	5 (3.6)	4 (16.7)	1 (4.3)
Hawaiian/Pacific Islander	1 (0.7)	0	0
Multiracial	1 (0.7)	0	0
Unknown	1 (0.7)	0	0
BMI (%)			
Underweight	7 (5.0)	0	0
Normal weight	91 (65.5)	7 (29.2)	10 (43.5)
Overweight	20 (14.4)	6 (25.0)	7 (30.4)
Obese	21 (15.1)	11 (45.8)	6 (26.1)

Patient characteristics for all patients.

Treatment characteristics and disease burden. At the time of CAR T-cell treatment at NCI, patients in our study had received a median of 5 (IQR, 3-6) prior therapy regimens, not including allogenic hematopoietic stem cell transplantation (allo-HSCT). In addition, 55 (39.6%) patients had received prior CAR T-cell therapy and 77 (55.3%) had received at least 1 allo-HSCT. However, a significantly lower proportion of Hispanic (35%; Table 2) and overweight/obese patients (34.1%; Table 3) received allo-HSCT compared with non-Hispanic (63.6%; $P = .004$) and nonoverweight/obese patients (64.3%; $P = .002$). Baseline disease burden in the bone marrow was M1 for 47 (33.8%), M2 for 16 (11.5%), and M3 for 76 (54.7%) patients and was similar across race, ethnicity (Table 2), and BMI (Table 3). Across trials, 50 (36.0%) patients received CD19 CAR, 71 (51.1%) received CD22 CAR, and 18 (12.9%) received CD19/22 bispecific CAR (Table 4).

Toxicity. Overall, 25 (18%) patients experienced grade ≥3 CRS (Table 4). Hispanic patients had >3 times greater odds of experiencing grade ≥3 CRS compared with White non-Hispanic patients (odds ratio [OR], 3.24; 95% confidence interval [CI], 1.23-8.54; $P = .001$). However, other non-Hispanic patients had similar odds of grade ≥3 CRS compared with White non-Hispanic patients (OR, 1.68; 95% CI, 0.46-6.08; $P = .43$). Similarly, the incidence of grade ≥3 CRS did not differ between females vs males (OR, 0.71; 95% CI, 0.261.94; $P = .50$) or between patients who were overweight/obese vs those who were not (OR, 0.92; 95% CI, 0.35-2.39; $P = .86$; Figure 2A). Severe CRS toxicity was more common in obese compared with overweight patients (supplemental Table 2). A sensitivity analysis of obese vs nonobese patients showed similar results (Table 5). However, continuous BMI measured in kg/m^2 was positively associated with grade ≥3 CRS (OR, 1.1; 95% CI, 1.02-1.18; $P = .01$; supplemental Table 3).

To further investigate the association between Hispanic ethnicity and severe CRS, we evaluated the relationship between additional factors and CRS severity. Although baseline disease burden in the bone marrow did not differ significantly by ethnicity (Table 2), high (M2/M3) disease burden was found to be associated with a higher incidence of grade ≥3 CRS compared with low (M1) disease burden (OR, 4.61; 95% CI, 1.30-16.3; $P = .02$), in line with previous studies examining clinical correlates of CAR-related toxicity.[31] Interestingly, we also found that adult patients with B-ALL had nearly 5 times greater odds experiencing grade ≥3 CRS compared with pediatric patients with B-ALL (OR, 4.94; 95% CI, 1.90-12.9; $P = .001$). Multivariable regression revealed that in a model accounting for age, race/ethnicity, and disease burden, all 3 variables were independently associated with higher odds of severe CRS (C-statistic = 0.82; Table 5). In a second multivariable model, continuous BMI measured in kg/m^2 was not significantly associated with CRS severity after adjusting for age, ethnicity, and

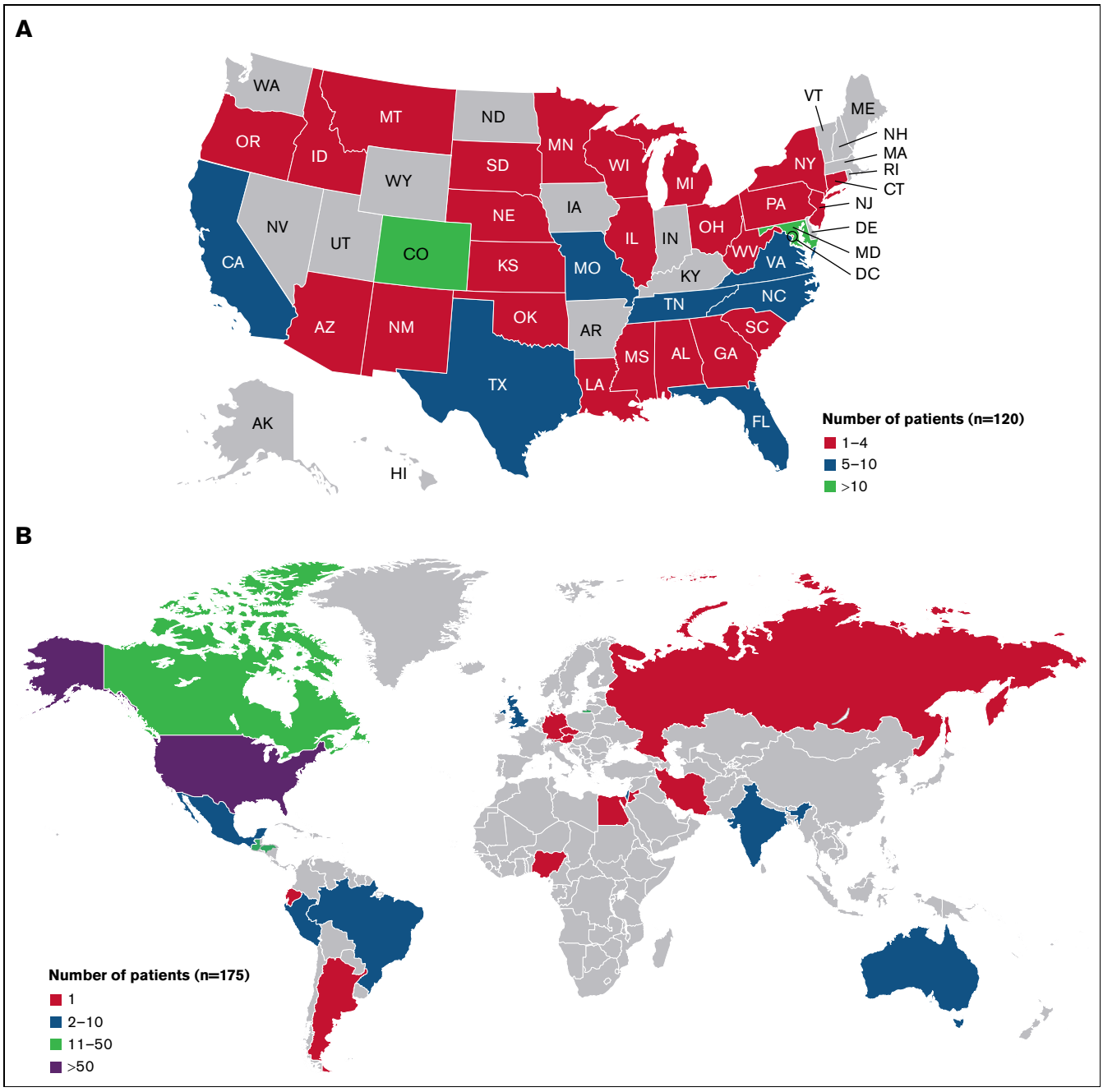

Figure 1. Map of geographic referral pattern. (A) Geographic origin of 120 domestic patients using ZIP codes. (B) Geographic origin of 175 patients. Eleven patients who were treated with 2 CAR constructs at separate times (for a total of 186 treatments) were counted once for geographic tallying. Maps generated at mapchart.net.

disease burden (supplemental Table 3). Strikingly, Hispanic patients who were overweight or obese had the greatest odds of severe CRS (Figure 3).

To verify that differences in CRS severity were not due to differences in CRS incidence overall, we performed a sensitivity analysis with CRS dichotomized as grade 1 to 5 vs grade 0. No differences in CRS incidence were found between groups. Furthermore, neither CAR T-cell construct ($P > .7$) nor CAR T-cell dose ($P = .96$) was associated with CRS severity in our study. Finally, as the management of CRS has shifted over the years to earlier and more frequent administration of tocilizumab,[32] we evaluated whether incidence of severe CRS in our study was related to treatment year; no relationship was observed for all patients with B-ALL (supplemental Figure 2). Among Hispanic patients with B-ALL, the incidence of severe CRS trended upward over time (supplemental Figure 3).

Neurotoxicity occurred in 29 (20.9%) patients (Table 4). Hispanic patients did not differ with respect to incidence of neurotoxicity compared with White non-Hispanic patients (OR, 0.95; 95% CI, 0.38-2.34; $P = .92$). Similarly, the odds of neurotoxicity in other

Table 2. B-ALL patient characteristics by race and ethnicity (n = 139)

	White non-Hispanic (n = 77)	Hispanic (n = 40)	Other non-Hispanic (n = 22)
Median age, y (IQR)	15.30 (10.70, 20.30)	15.60 (9.17, 21.38)	12.90 (7.03, 20.35)
Male (%)	57 (74.0)	29 (72.5)	12 (54.5)
BMI (%)			
Underweight	5 (6.5)	0	2 (9.1)
Normal weight	51 (66.2)	27 (67.5)	13 (59.1)
Overweight	12 (15.6)	4 (10.0)	4 (18.2)
Obese	9 (11.7)	9 (22.5)	3 (13.6)
Disease burden (%)			
M1	28 (36.4)	13 (32.5)	6 (27.3)
M2	8 (10.4)	5 (12.5)	3 (13.6)
M3	41 (53.2)	22 (55.0)	13 (59.1)
Prior allo-HSCT (%)	52 (67.5)	14 (35.0)	11 (50.0)
Prior CART (%)	35 (45.5)	14 (35.0)	6 (27.3)

non-Hispanic patients were statistically comparable to White non-Hispanic patients (OR, 0.33; 95% CI, 0.07-1.54; $P = .16$). In contrast, males had >3 times greater odds than females for neurotoxicity (OR, 3.17; 95% CI, 1.03-9.78; $P = .05$). Neurotoxicity incidence was similar between patients who were overweight/obese and those who were not (OR, 0.89; 95% CI, 0.36-2.21; $P = .80$; Figure 2B). Other patient characteristics, including baseline disease burden, age, and CAR T-cell construct, were not associated with incidence of neurotoxicity (supplemental Table 4).

Efficacy. Overall, 94 (67.6%) patients achieved CR (Table 4). CR rates were comparable between Hispanic vs White non-Hispanic patients (OR, 0.67; 95% CI, 0.30-1.50; $P = .33$); other non-Hispanic vs White non-Hispanic patients (OR, 0.81; 95% CI, 0.29-2.25; $P = .67$); males vs females (OR, 0.60; 95% CI, 0.26-1.37; $P = .22$); and patients who were overweight/obese vs those who were not (OR, 0.74; 95% CI, 0.34-1.60; $P = .44$; Figure 2C). Further analysis revealed that only M2/M3 vs M1 disease burden was well associated with lower CR rates (OR, 0.38; 95% CI, 0.16-0.88; $P = .02$; supplemental Table 5).

Table 3. B-ALL patient characteristics by BMI (n = 139)

	Not overweight/obese (n = 98)	Overweight/obese (n = 41)
Median age, y (IQR)	15.25 (9.70, 20.38)	14.70 (8.40, 22.80)
Male (%)	67 (68.4)	31 (75.6)
Race/ethnicity		
White non-Hispanic (%)	56 (57.1)	21 (51.2)
Hispanic (%)	27 (27.6)	13 (31.7)
Other non-Hispanic (%)	15 (15.3)	7 (17.1)
Disease burden (%)		
M1	34 (34.7)	13 (31.7)
M2	12 (12.2)	4 (9.8)
M3	52 (53.1)	24 (58.5)
Prior allo-HSCT (%)	63 (64.3)	14 (34.1)
Prior CART (%)	42 (42.9)	13 (31.7)

Because of the limited representation of Black and African American patients in our trials, which impaired our ability to perform inferential statistical comparisons for this specific group, we descriptively evaluated outcomes of the 5 Black patients with B-ALL in our study. Four (80%) patients achieved CR, including 1 patient with M3 disease burden, and none experienced neurotoxicity or grade ≥3 CRS. Among 14 Asian patients, 7 (50%) achieved CR, 2 (14.3%) experienced grade ≥ 3 CRS, and 1 (7.1%) experienced neurotoxicity.

Overall survival (n = 128). Median OS was 12.2 months (Figure 4A). However, no statistically significant differences in survival were observed between male vs female patients (11.8 vs 14.9 months; $P = .66$; Figure 4B); Hispanic vs White non-Hispanic patients (14.6 vs 12.8 months; Figure 4C); other non-Hispanic vs White non-Hispanic patients (12.8 vs 7.9 months; Figure 4C); or overweight/obese patients vs nonoverweight/obese patients (14.9 vs 11.9 months; $P = .28$; Figure 4D). By the end of the study period, 3 (60%) Black patients (supplemental Figure 4) and 10 (71.4%) Asian patients had died.

Cohort with MM (n = 24)

All MM patients received BCMA CAR. Six (25%) experienced severe CRS, including 1 (33%) Hispanic patient and 4 (23.5%) overweight/obese patients. Neurotoxicity occurred in 3 (12.5%) patients, none of whom were Hispanic and all of whom were overweight/obese. Only 2 (8.3%) patients with MM achieved CR, one of whom was overweight/obese and one of whom was Black (nonoverweight/obese) (supplemental Table 6). Among the 4 Black patients, none experienced severe CRS or any grade of neurotoxicity.

Cohort with NHL (n = 23)

All but 1 NHL patient received CD19 CAR therapy. Severe CRS toxicity occurred in 6 (26.1%) of the NHL patients, including 1 (50%) Hispanic patient and 5 (38.5%) overweight/obese patients. Three (13%) patients, all of whom were overweight/obese and one of whom was Hispanic, experienced neurotoxicity. Ten (43.5%) patients achieved CR, including 1 (50%) Hispanic and 7 (53.8%) overweight/obese patients (supplemental Table 6). One Black patient with Burkitt lymphoma treated on the CD19/22 CAR T-cell trial[33] did not achieve CR nor experienced neurotoxicity or CRS and died of progressive disease.

Discussion

CAR T-cell therapy has transformed outcomes for relapsed/refractory hematologic malignancies, yet whether its benefits apply equally to diverse patient populations and patients with common comorbidities, such as obesity, is poorly understood. Given the tremendous potential of CAR T-cell therapy to overcome chemotherapy-resistant and refractory disease, understanding whether its benefits extend equally to racial and ethnic minorities and patients with obesity is of critical importance to assessing the generalizability of existing outcome data for this novel cancer treatment modality and potentially improving outcomes for the highest-risk populations.

Table 4. CAR treatment, toxicity, and response of patients with B-ALL

n (%)	Overall (n = 139)	Overweight/obese (n = 41)	Hispanic (n = 40)	Other non-Hispanic (n = 22)
CAR construct				
CD19	50 (36.0)	15 (36.6)	18 (45.0)	7 (31.8)
CD22	71 (51.1)	19 (46.3)	15 (37.5)	12 (54.5)
CD19/22	18 (12.9)	7 (17.1)	7 (17.5)	3 (13.6)
CRS ASTCT grade				
None	33 (23.7)	10 (24.4)	12 (30.0)	6 (27.3)
1	47 (33.8)	17 (41.5)	9 (22.5)	6 (27.3)
2	34 (24.5)	7 (17.1)	7 (17.5)	6 (27.3)
3	20 (14.4)	6 (14.6)	10 (25.0)	3 (13.6)
4	5 (3.6)*	1 (2.4)	2 (5.0)	1 (4.5)
Developed neurotoxicity	29 (20.9)	8 (19.5)	9 (22.5)	2 (9.1)
CR				
Yes	94 (67.6)	26 (63.4)	25 (62.5)	14 (63.6)
No	44 (31.7)	15 (36.6)	15 (37.5)	7 (31.8)
Not evaluable	1 (0.7)*	0	0	1 (4.5)

*One patient died of toxicity with grade 4 CRS and grade 5 capillary leak syndrome.

One of the overarching challenges in addressing this question has been the underrepresentation of minority populations in both early-phase clinical trials and pivotal registration studies.[34] In 2 landmark phase 3 trials in the United States, representing the very first randomized studies of CAR T-cell therapy to date, ~80% of patients were White and <10% were Hispanic or Black, a stark contrast from the current demographic landscape.[3,35] Despite our center being a federally funded institution that enrolls children and young adults on clinical trials independent of insurance coverage with wide national and international recruitment, our study also shows underrepresentation of Black patients, limiting our ability to discern outcomes by race. This is consistent with generally lower enrollment of Black Americans in cancer clinical trials,[36] particularly on phase 1 trials where efficacy is not a primary objective, which poses a critical additional barrier.[37] Understanding and overcoming barriers to enrollment of minority populations remains an active effort.

Recent retrospective studies have attempted to address this gap in knowledge. A study of 185 patients with B-ALL treated with commercial CD19 CAR therapy (tisagenlecleucel) demonstrated that Black children and young adults (n = 11, 5.9%) were less likely to receive CAR infusion and had worse survival outcomes compared with non-Black patients.[26] On the other hand, a study of 78 adult patients with NHL showed no differences in toxicity, efficacy, or survival between obese and nonobese patients receiving CD19 CAR T-cell therapy.[38] Our study, which examined the impact of race, ethnicity, and obesity on CAR T-cell toxicity and efficacy outcomes in both adult and pediatric patients with diverse geographic backgrounds across multiple hematologic malignancies and CAR T-cell constructs, serves to add to these limited data.

We show that CR rates with CAR T-cell therapy in this heavily pretreated population were high in B-ALL but limited in NHL and MM, accounting for the phase I and dose-escalation nature of our trials.[39-43]

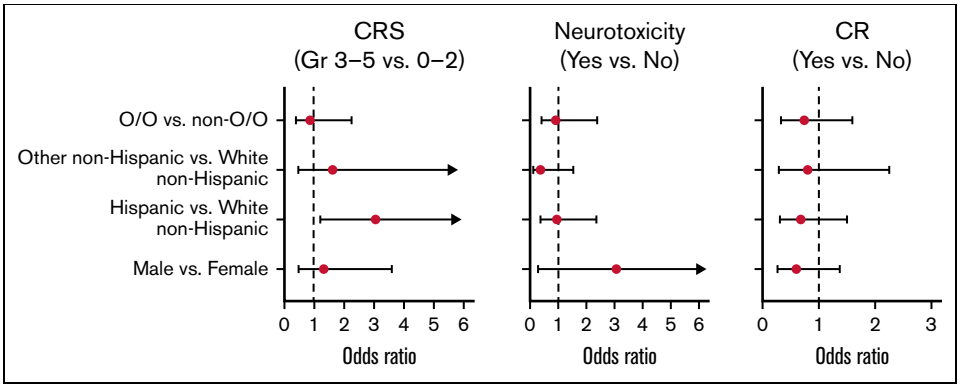

Figure 2. Forest plots of toxicity and efficacy by race, ethnicity, sex, and BMI among patients with B-ALL. (A) ORs of severe CRS. (B) ORs of neurotoxicity. (C) ORs of CR. ORs were calculated from simple (univariate) logistic regression models with intercept term. Interval bands represent 95% CIs for the point estimates. Arrowheads indicate CI extending beyond axis range. Overweight/obese (O/O) defined as BMI ≥ 25 in patients aged ≥20 years and BMI ≥ 85th percentile in patients aged 2 to 20.

Table 5. Odds of CRS (grade 3 to 5 vs 0 to 2) in B-ALL (n = 139)

	Univariate		Multivariable	
Variable (risk group vs ref)	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age (continuous, y)	**1.13 (1.06-1.21)**	**<.001**	**1.15 (1.07-1.23)**	**<.001**
≥18 y (adult) vs <18 y (pediatric)	**4.94 (1.90-12.8)**	**.001**	–	–
Sex (male vs female)	1.40 (0.52-3.82)	.51	–	–
Race/ethnicity (Hispanic vs White NH)	**3.24 (1.23-8.54)**	**.02**	**4.51 (1.46-13.9)**	**.001**
Other non-Hispanic vs White NH	1.68 (0.46-6.08)	.43	2.0 (0.48-8.41)	.34
Prior allo-HSCT (yes vs no)	**0.38 (0.16-0.93)**	**.04**	–	–
Prior CART (yes vs no)	0.42 (0.16-1.13)	.08	–	–
Disease burden (M2/3 vs M1)	**4.61 (1.30-16.3)**	**.02**	**5.48 (1.40-21.5)**	**.01**
BMI (O/O vs non-O/O)	0.92 (0.35-2.40)	.86	–	–
Obese vs nonobese	2.1 (0.72-6.1)	.18	–	–
CAR (CD22 vs CD19)	0.93 (0.36-2.4)	.88	–	–
CD19/22 vs CD19	1.30 (0.35-4.90)	.7	–	–

Association of patient, treatment, and disease characteristics with CRS severity. Univariate and multivariable ORs were calculated using logistic regression models. The significance of the 'bold' font is to signify those which have a significant p-value. The "dash" indicates that the particular variable that it was associated with was not carried forward to the multivariable analysis.

Importantly, no differences in CR rates were observed by sex, ethnicity, race, or BMI in patients with B-ALL. Moreover, among patients with B-ALL, overall survival was similar between demographic groups. These results differ from outcomes observed for Hispanic patients and patients with obesity in previous studies with standard chemotherapy. A secondary analysis of 794 patients, including 150 Hispanic patients, from a phase 3 clinical trial for B-ALL in children at Dana-Farber demonstrated inferior overall survival in Hispanic patients.[44]

With respect to BMI, we similarly demonstrate comparable remission rates and survival outcomes between obese vs nonobese patients. Overall, this suggests CAR T-cell therapy may be uniquely situated to provide substantial benefit among high-risk patient populations who are more likely to be chemotherapy resistant, highlighting the need to improve access to CAR T-cell therapy and clinical trials in these groups. In this regard, we unexpectedly identified that Hispanic patients and those with obesity were significantly less likely to have received prior HSCT, suggesting either issues with access to HSCT or having chemotherapy-resistant disease that precluded HSCT–warranting further study.

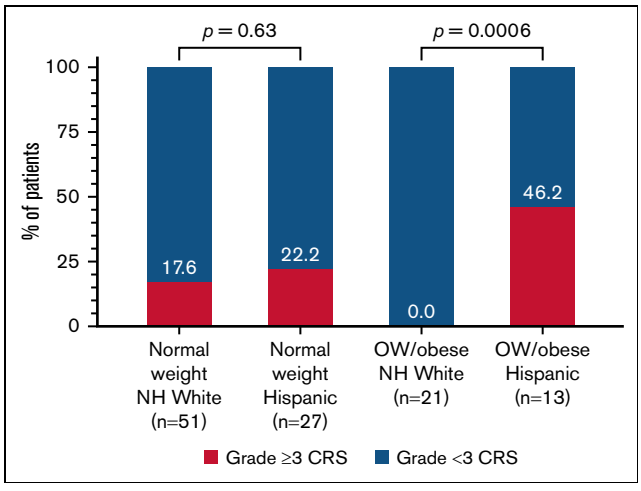

Figure 3. CRS severity stratified by ethnicity and BMI. Statistical comparison performed using χ^2 test. NH, non-Hispanic; OW, overweight.

Despite similar efficacy across demographic groups, our study found a consistent association between Hispanic ethnicity and severe CRS. Although validated models to predict CRS severity following CAR therapy are lacking, 2 strong predictors include baseline bone marrow disease burden in B-ALL and CAR T-cell dose.[31] Neither accounted for the trend found in our study. Although high disease burden was associated with grade ≥3 CRS, multivariable analysis, including disease burden, age, and Hispanic ethnicity, found all three to be independently associated with severe CRS. Despite changes in CRS management since the debut of CAR T-cell therapy, we did not observe a consistent trend of CRS severity by treatment year in our B-ALL cohort.

Importantly, other factors not evaluated in this study, such as lymphodepletion regimens and CAR manufacturing nuances,[45] have also been implicated with CRS severity, and therefore, additional work is required to elucidate whether these factors might impact the toxicity disparities we found. Notably, extremes of BMI have been associated with greater toxicity with conventional leukemia therapy,[46] and although our study failed to show an association between BMI and CRS severity in general, we did find Hispanic patients who were overweight or obese were at the highest risk for severe CRS in our cohort. The basis for this disparity is unclear and warrants further investigation, but previous work in the health disparities space points to multifactorial causes, including differences in cancer biology and preexisting comorbidities in addition to structural barriers to equitable care.[47] How this impacts dosing considerations in obese patients receiving CAR T-cells is an additional question that should be more broadly studied. Similarly, our finding that adult patients with B-ALL were at higher risk for severe CRS compared with pediatric patients with B-ALL independent of ethnicity and disease burden warrants further investigation with larger studies.

The incidence of neurotoxicity was comparable to the rate of severe CRS in our study. However, we found no significant associations

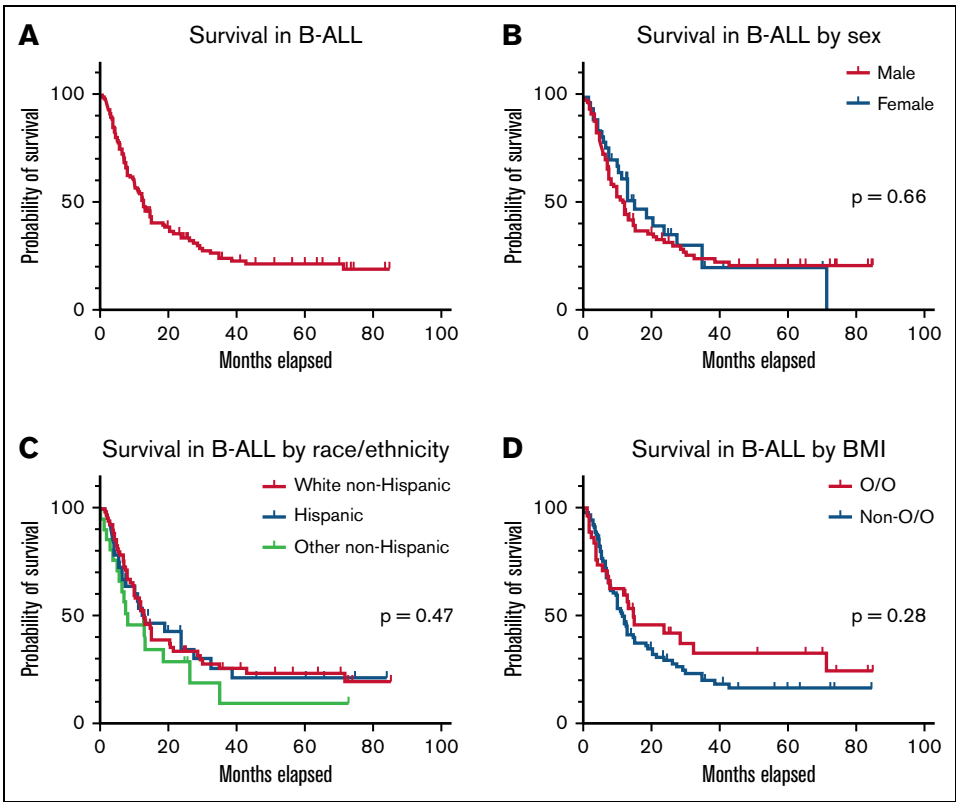

Figure 4. Kaplan-Meier survival curves of patients with B-ALL by race, ethnicity, sex, and BMI. (A) Survival of entire B-ALL cohort. (B) Survival comparison by sex. (C) Survival comparison by race/ethnicity. (D) Survival comparison by BMI. *P* values calculated using log rank method. t = 0 corresponds to time of last CAR T-cell infusion. Overweight/obese (O/O) defined as BMI ≥ 25 in patients age ≥20 years and BMI ≥ 85th percentile in patients aged 2 to 20.

between ethnicity or BMI and neurotoxicity. The basis for higher incidence of neurotoxicity in male compared with female patients in our study is unknown, although the CI for OR estimate is wide because of the sample size of our study. Previous work has identified common predictors, such as baseline disease burden in B-ALL, for CRS and neurotoxicity.[31] Interestingly, baseline disease burden was not significantly associated with neurotoxicity on univariate analysis in our B-ALL cohort, suggesting other drivers of neurotoxicity may be present, but also aligning with the overall lower neurotoxicity rates seen across our phase 1 CAR T-cell trials for B-ALL.[48,49] Among these drivers may be neurologic comorbidities present prior to receipt of CAR T-cell therapy. Ongoing work by our group and others has aimed to better understand the determinants of neurotoxicity.

Our study has several limitations, including those inherent to the retrospective nature of this analysis. Patients with B-ALL in our cohort were heavily pretreated before receiving CAR T-cell therapy, with a large percentage of patients having received CAR T-cell therapy or HSCT prior to enrollment in our trials, although CAR T-cell reinfusions (=infusion of the same product) were specifically excluded from this analysis for this reason.[50] Previous studies examining the association of obesity with cancer outcomes have typically used BMI at diagnosis, but this was not feasible in our study given that the majority of patients were diagnosed at other institutions many years prior to enrollment in our clinical trials. Although obesity of varying classes may be of interest within the field,[51] our analysis is limited by insufficient patients to adequately examine differences between these patient populations, and prospective evaluations may be more definitive.

Socioeconomic status, particularly with respect to family and neighborhood, is also known to significantly contribute to disparities in cancer outcomes,[52] but we were unable to adequately account for this due to limited documentation patient insurance status. These factors may represent significant confounders we were unable to control for. The relatively small number of subjects in our study, particularly with respect to representation of Black patients, limits our ability to perform more comprehensive demographic analyses and reduces our power to detect smaller but clinically meaningful differences in efficacy outcomes across subgroups. As patients referred to our institution had multiply refractory disease, overall survival is likely not reflective of outcomes in patients who are treated earlier in their disease course, which is particularly relevant as CAR T cells move earlier into treatment paradigms. Last, although our results highlight the potential of CAR T-cell therapy to improve outcomes in populations who have worse chemotherapy outcomes, it is important to recognize combating cancer health disparities will require a multifaceted approach that incorporates not only better access to emerging therapies such as CAR T cells but also improved prevention and relapse mitigation strategies.

In conclusion, based on this retrospective analysis across 5 phase 1 clinical trials for both adult and pediatric patients with 3 hematologic malignancies treated with CAR T-cell therapy, we show that

Hispanic patients are more likely to experience severe CRS after CAR T-cell therapy, even after adjusting for baseline B-ALL disease burden and age. Future larger studies are needed to both validate these findings and further characterize the factors underlying differential toxicity among demographic groups, with the ultimate goal of implementing mitigation strategies that reduce toxicity while maintaining efficacy. Despite this discrepancy in toxicity, efficacy across racial/ethnic groups and BMI classes was comparable. Given that Hispanic patients and patients with obesity are more likely to experience chemotherapy-resistant or refractory disease, our findings suggest that CAR T-cell therapy may provide substantial benefit to these high-risk groups. Thus, efforts to identify barriers in representation of racial/ethnic minorities and other high-risk groups in clinical trials in general, and CAR T-cell therapy trials in particular, should be prioritized.

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Authorship

Contribution: A.J.F., P.B., and N.N.S. designed the study and performed primary data analysis; A.J.F. and N.N.S. wrote the first version of the manuscript; J.A.L., P.B., and B.Y. provided critical input for the data analysis; S.M.S. conducted statistical analysis and provided critical input on select sections within the manuscript; J.A.L., T.F., L.L., C.L.M., D.W.L., T.J.F., H.S., J.B., B.Y., L.M., J.K., and N.N.S. provided patient care, oversight of the clinical trials for which the subjects were enrolled on, and primary data that contributed to this analysis. No nonauthor wrote the first draft or any part of the paper. All authors contributed to the review of the final manuscript and have agreed to be coauthors.

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