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Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report

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abstract

PURPOSE Tisagenlecleucel is a CD19-specific chimeric antigen receptor T-cell therapy, US Food and Drug Administration–approved for children, adolescents, and young adults (CAYA) with relapsed and/or refractory (RR) B-cell acute lymphoblastic leukemia (B-ALL). The US Food and Drug Administration registration for tisagenlecleucel was based on a complete response (CR) rate of 81%, 12-month overall survival (OS) of 76%, and event-free survival (EFS) of 50%. We report clinical outcomes and analyze covariates of outcomes after commercial tisagenlecleucel.

METHODS We conducted a retrospective, multi-institutional study of CAYA with RR B-ALL across 15 US institutions, who underwent leukapheresis shipment to Novartis for commercial tisagenlecleucel. A total of 200 patients were included in an intent-to-treat response analysis, and 185 infused patients were analyzed for survival and toxicity.

RESULTS Intent-to-treat analysis demonstrates a 79% morphologic CR rate (95% CI, 72 to 84). The infused cohort had an 85% CR (95% CI, 79 to 89) and 12-month OS of 72% and EFS of 50%, with 335 days of median follow-up. Notably, 48% of patients had low-disease burden (< 5% bone marrow lymphoblasts, no CNS3, or other extramedullary disease), or undetectable disease, pretisagenlecleucel. Univariate and multivariate analyses associate high-disease burden (HB, ≥ 5% bone marrow lymphoblasts, CNS3, or non-CNS extramedullary) with inferior outcomes, with a 12-month OS of 58% and EFS of 31% compared with low-disease burden (OS; 85%, EFS; 70%) and undetectable disease (OS; 95%, EFS; 72%; $P < .0001$ for OS and EFS). Grade ≥ 3 cytokine release syndrome and neurotoxicity rates were 21% and 7% overall and 35% and 9% in patients with HB, respectively.

CONCLUSION Commercial tisagenlecleucel in CAYA RR B-ALL demonstrates efficacy and tolerability. This first analysis of commercial tisagenlecleucel stratified by disease burden identifies HB preinfusion to associate with inferior OS and EFS and increased toxicity.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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BACKGROUND

Survival in pediatric B-cell acute lymphoblastic leukemia (B-ALL) has improved dramatically over the past 50 years[1-4]; however, relapsed and/or refractory (RR) B-ALL remains a dominant cause of pediatric cancer–related mortality.[1,5-7] Chimeric antigen receptor (CAR) T cells targeting CD19 have proven to be effective in achieving early responses in pediatric B-ALL with complete response (CR) rates of 65%-90% across varied CAR constructs and institutions.[8-12] The landmark ELIANA trial studying tisagenlecleucel, autologous CD19-specific CAR T cells, demonstrated an 81% CR rate in 75 infused children, adolescents, and young adults (CAYA; eligibility included ≥ 3 years at screening, ≤ 21 years at diagnosis, and ≥ 5% bone marrow [BM] lymphoblasts at screening). Twelve-month overall survival (OS) and event-free survival (EFS) rates were 76% and 50%, respectively. Significant toxicity was reported with

CONTEXT

Key Objective

After tisagenlecleucel commercialization, cross-institutional practices relating to tisagenlecleucel administration are heterogeneous and data-capturing is limited. Our key objective was to interrogate data from the commercial pediatric tisagenlecleucel experience to establish outcomes in the real-world setting and understand variables affecting post–chimeric antigen receptor outcomes. To approach this, we developed a national consortium, permitting cross-institutional reporting and analysis. Beyond overall outcome reporting, we distinctly report response, toxicity, and survival outcomes, as stratified by disease burden.

Knowledge Generated

Univariate and multivariate analyses studying covariates of response, toxicity, and survival demonstrate that patients with high-disease burden, defined by ≥ 5% bone marrow lymphoblasts, any circulating lymphoblasts and/or CNS3, or non-CNS extramedullary disease, have a decreased response rate, increased toxicity, and decreased overall and event-free survival.

Relevance

We identify patients entering tisagenlecleucel with high-disease burden to be a high-risk patient population who may benefit from further interventional strategies to consolidate chimeric antigen receptor–mediated outcomes.

49% ≥ grade 3 cytokine release syndrome (CRS), as graded by UPENN criteria and 13% ≥ grade 3 neurotoxicity,[9] as graded by common terminology criteria for adverse events. This study led to US Food and Drug Administration approval of tisagenlecleucel (Kymriah) in August 2017 for the treatment of CAYA < age 26 years, with ≥ 2nd RR B-ALL.

After tisagenlecleucel commercialization, cross-institutional clinical practice and data-capturing have been heterogeneous and limited. To understand the functionality of commercial tisagenlecleucel, we conducted a retrospective, multi-institutional study measuring the relationship between baseline characteristics and clinical outcomes.

METHODS

Study Design

We formed a national consortium comprising 15 pediatric centers delivering standard-of-care tisagenlecleucel (Data Supplement, online only). Centers obtained independent institutional review board approval, collecting deidentified data in a Health Insurance Portability and Accountability Act–compliant, REDCap database. Patients with RR B-ALL who underwent leukapheresis shipment to Novartis (Hanover, NJ) for commercial tisagenlecleucel manufacturing, from August 30, 2017, through March 6, 2020, were included in an intent-to-treat response analysis (Table 1). All infused patients, including those on an expanded managed access protocol (MAP, NCT03601442) or with individual investigational new drug (s-IND) approval, with 28 days of minimum follow-up as of data cutoff, were included for response, toxicity, and survival analyses. MAP/s-IND was included because of intent for commercial product and previous work establishing comparable outcomes with products meeting manufacturing specifications.[13]

Study Aims and Clinical Outcome Assessment

Our primary aim was to establish overall day 28 (d28) response rate after standard-of-care tisagenlecleucel, as measured by BM and/or peripheral blood morphology and minimal residual disease (MRD) by flow cytometry, with negativity defined by the performing laboratory's threshold. Extramedullary (EM) disease was assessed by CSF, imaging, and/or physical examination. CR is defined as < 5% BM lymphoblasts and absence of circulating lymphoblasts and EM disease. Secondary aims included analysis of OS and EFS at 6 and 12 months after tisagenlecleucel. OS and EFS were measured from time of CAR infusion to occurrence of event or censored at the last follow-up. OS considered all-cause death as event, and EFS events included lack of d28 CR, relapse, secondary malignancy, and death. We establish duration of remission (DOR) and duration of B-cell aplasia (DBA), as measured from CAR infusion in only patients achieving CR. Although DOR and DBA are reported from CAR infusion, establishment of CR and B-cell aplasia (BCA) was only confirmed at d28 (Data Supplement). BCA is defined by CD19 recovery, as per institutional threshold. Because CRS grading algorithms changes over time, CRS was retrospectively graded according to the American Society for Transplantation and Cellular Therapy (ASTCT)[14] for all patients. Neurotoxicity was graded by ASTCT[14] (69%), CAR-related encephalopathy syndrome (CRES)[15] (16%), and others (16%), per institutional standard. We additionally analyzed the secondary end point, time to relapse and/or second malignancy, treating nonrelapse death, and hematopoietic stem cell transplantation (HSCT) as competing risks.

Our exploratory aim was to evaluate risk factors for response and survival, including baseline age at diagnosis, sex, cytogenetics, prior therapy lines, prior HSCT, prior CD19-directed therapy, disease burden, time from diagnosis to CAR infusion, and RR status. A distinct therapy line was

TABLE 1. Baseline Patient Characteristics

Characteristic	Value (total ITT), N = 200	Value (infused), n = 185	Value (noninfused), n = 15
Age at infusion, years			
Median (range)		12 (0-26)	
Sex, No. (%)			
Male	120 (60)	111 (60)	9 (60)
Female	80 (40)	74 (40)	6 (40)
Race/ethnicity, No. (%)			
Non-Hispanic White	93 (47)	90 (49)	3 (20)
Hispanic	75 (38)	70 (38)	5 (33)
Black/African American	11 (6)	7 (4)	4 (27)
Asian	9 (5)	7 (4)	2 (13)
Mixed race	5 (3)	4 (2)	1 (7)
Unknown	7 (4)	7 (4)	0
Disease subtype, No. (%)			
Cytogenetics			
High risk	70 (35)	66 (36)	4 (27)
Ph-positive (p190 and p210)	10 (5)	10 (5)	0
Ph-like	26 (13)	24 (13)	2 (13)
MPAL	2 (1)	2 (1)	0
Low risk	26 (13)	24 (13)	2 (13)
Intermediate risk	52 (26)	49 (26)	3 (20)
Unknown	52 (26)	46 (25)	6 (40)
Prior lines of therapy, No. (%)			
1	11 (6)	9 (5)	2 (13)
2	48 (24)	47 (25)	1 (7)
3	60 (30)	58 (31)	2 (13)
4	40 (20)	37 (20)	3 (20)
5	18 (9)	16 (9)	2 (13)
> 5	23 (12)	18 (10)	5 (33)
Disease status/CAR indication, No. (%)			
Refractory disease without relapse	31 (16)	30 (16)	1 (7)
One relapse	74 (37)	68 (37)	6 (40)
Two relapses	73 (37)	68 (37)	5 (33)
Three relapses	8 (4)	8 (4)	0
> 3 relapses	11 (6)	10 (5)	1 (7)
Unknown	3 (2)	1 (0.5)	2 (13)
Prior allogeneic HSCT, No. (%)			
Yes	52 (26)	47 (35)	5 (33)
Prior CD19 therapy, No. (%)			
Prior blinatumomab	40 (20)	34 (18)	6 (40)
Prior CD19 CAR	6 (3)	6 (3)	0
Prior CD22 therapy, No. (%)			
Prior inotuzumab	39 (20)	31 (17)	8 (53)
Prior CD22 CAR	3 (2)	3 (2)	0

Abbreviations: CAR, chimeric antigen receptor; HSCT, hematopoietic stem cell transplantation; ITT, intent to treat; MPAL, mixed phenotype acute leukemia.

defined as initiation of a new treatment plan because of disease recurrence, refractory disease, or toxicity. Time from diagnosis to CAR infusion, number of prior therapy lines, and number of relapses are considered as continuous predictors in our multivariate Cox model while age at diagnosis was categorized into groups using the cut points that reflect known clinical risk groups: 0-2, 3-9, 10-12, 13-20, and ≥ 21 years.

Univariate and multivariate findings drove detailed outcome analysis in patients with variable disease burden, as reported at the time of last pre-CAR disease evaluation. High-disease burden (HB) is defined by ≥ 5% BM lymphoblasts, any peripheral blood lymphoblasts, CNS3 status, or non-CNS EM site of disease; low-disease burden (LB) is defined by morphologic or flow cytometry detectable BM or CNS disease not meeting HB criteria, and patients without morphologic or flow cytometry detectable disease or EM disease were categorized as undetectable (UD).

Statistical Analysis

We report frequency and percent for d28 CR, CRS, and neurotoxicity with Fisher's exact test to test differences between subgroups. Kaplan-Meier (KM) curves were plotted by baseline characteristics and compared using log-rank tests for OS, EFS, DOR, and DBA. Continuous factors (prior therapy lines and number of prior relapses) were categorized in KM curves for descriptive visualization but were kept as continuous in subsequent regression models. A multivariate Cox model for OS was constructed, including all baseline factors except cytogenic risk and EM disease because of data missingness. The Schoenfeld residual test was used for assessing proportional hazards assumption.

In the exploratory analysis of time to relapse and/or second malignancy treating nonrelapse death and HSCT as competing risks, we generated cumulative incidence curves for each competing event. We used a cause-specific hazard regression model to estimate biological associations between various risk factors and the cause-specific hazard of relapse.[16-18] We additionally used KM curves to report OS, EFS, and DOR from the time of HSCT in patients receiving HSCT while in CAR-mediated remission.

RESULTS

Patients

A total of 200 patients who underwent cell shipment to Novartis for planned standard-of-care tisagenlecleucel therapy were included in this analysis. Of 200 patients, 92.5% (185) of patients were infused and 7.5% (15) were not infused. Eighty-seven percent (161) of infused products met manufacturing release criteria, and 13% (24) were delivered on the MAP or with s-IND approval (Fig 1). Seventy-one percent (17) of MAP/sIND products were nonconforming because of subthreshold viability, all with viability ranging from 70% to 80%.

The median follow-up from tisagenlecleucel was 335 days (range, 6-863; follow-up < d28 reflect early deaths). The median age at infusion was 12 years (range, 0-26). Thirteen patients were < 3 years at the time of infusion, and six were > 21 years at the time of diagnosis. Table 1 includes expanded patient and disease characteristics. Sixteen percent (30) of patients were treated for up-front refractory disease (seven with ≥ 5% and 23 with < 5% end-of-induction BM lymphoblasts) and 83% (154) for relapsed disease (67 in first relapse and 87 in ≥ second relapse). One patient was treated upfront because of high-risk treatment-related B-ALL and HSCT contraindication. Reasons for treatment in the first relapse include chemorefractoriness

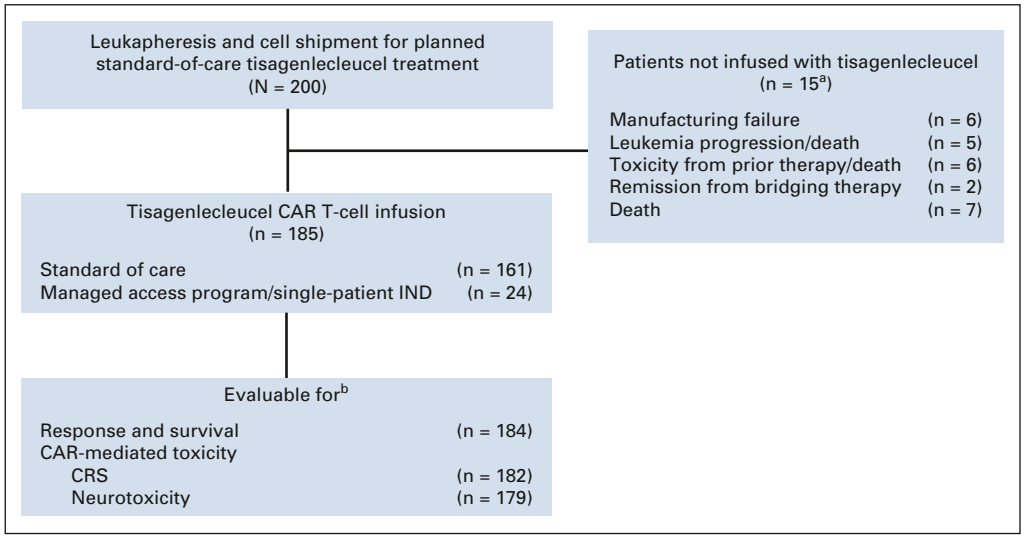


FIG 1. Patient flow diagram. [a]Patients had concurrent disease progression, toxicities from prior therapy and/or death, therefore cumulative sum > 15. [b]Patients excluded because of incomplete reporting. CAR, chimeric antigen receptor; CRS, cytokine release syndrome; IND, investigational new drug.

(54), prior HSCT (9), HSCT otherwise contraindicated (15; 12 of whom were additionally chemorefractory), and salvage chemotherapy contraindicated (1; Data Supplement).

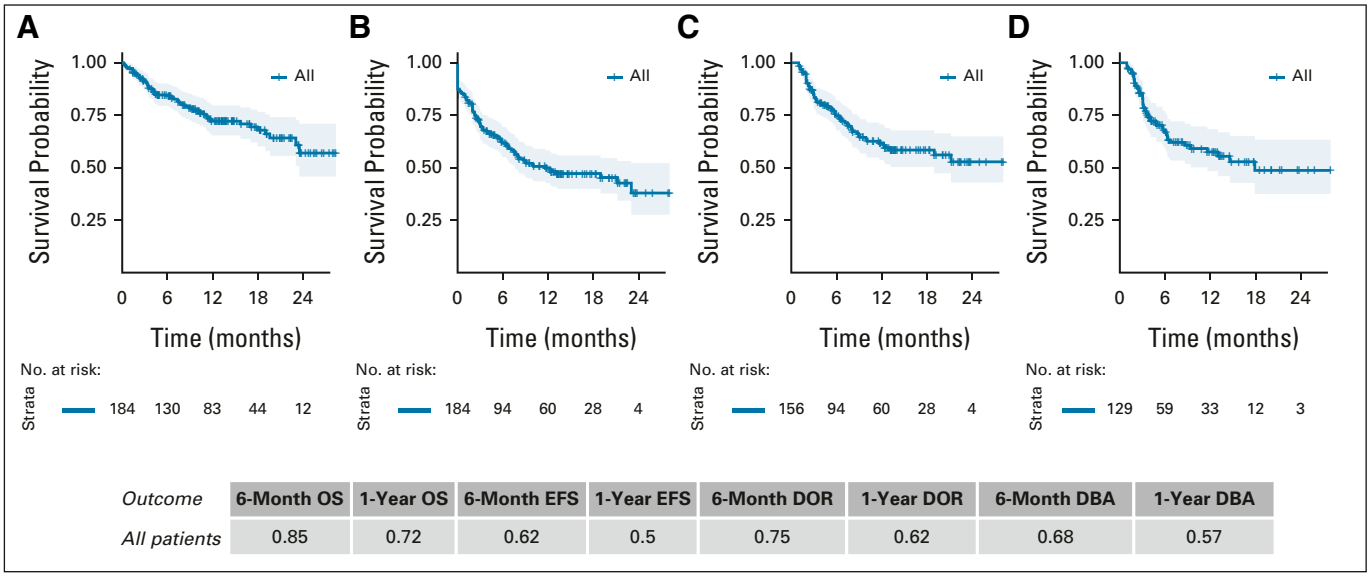
Patients underwent a median of three prior therapy lines (range, 1-10) with a median duration of 33 months (range, 3-171) between diagnosis and infusion. Twenty-one percent (38) of patients received pretisagenlecleucel CD19-targeted therapies, and 18% (34) received prior CD22-targeted therapies. Twenty-five percent (47) received HSCT pretisagenlecleucel, five of whom received > 1 HSCT. Among infused patients, 51% (94) had HB, 22% (41) had LB, and 25% (46) had UD disease; four had indeterminate disease burden. Seventeen percent (13) had CNS disease (CNS2 [n = 7]; CNS3 [n = 6]), and 8% (15) had non-CNS EM disease (craniofacial [6], bone [3], testes [3], soft tissue [3], renal [2], skin [1], ocular [1], and lung [1]). Fifty-nine percent (105) had no bridging therapy, and 41% (73) had bridging therapy between disease burden assessment and lymphodepletion, with a median duration between assessment and tisagenlecleucel in these cohorts of 2 weeks (range, 0-12) and 8 weeks (range, 1-22), respectively. Details of lymphodepletion, apheresis, CAR product, and infusion are included in the Data Supplement.

Efficacy

Intent-to-treat response analysis, excluding patients non-infused because of CR from prior therapy, demonstrated a 79% (156 of 197; 95% CI, 72 to 84) d28 CR rate. Of 184 infused evaluable patients, d28 CR rate was 85% (156 of 184; 95% CI, 79 to 89). A similar CR rate (83%) was observed in the subgroup of patients receiving MAP/s-IND products. Among 134 patients infused with detectable disease at pretisagenlecleucel evaluation, the CR rate was 81% (108 of 134; 95% CI, 73 to 86). Of infused patients achieving morphologic CR, MRD testing by flow cytometry was available for 98% (153) with 97% (148) achieving MRD-negative CR. MRD testing using next-generation sequencing was available for 17% (32) of infused patients, of whom five with CR by morphology and flow cytometry had detectable next-generation sequencing MRD.

Median OS has not yet been reached. Among 184 infused, evaluable patients, 6-month OS was 85% and 12-month OS was 72%. Six-month EFS was 62%, and 12-month EFS was 50%. Of 156 patients with d28 CR, DOR at 6 and 12 months was 75% and 62%, respectively (Fig 2). Thirty-seven percent (57 of 156) of responders experienced relapse. The median time from infusion to relapse was 101 days (range, 30-645). At the time of relapse, 41% (22 of 52) of evaluable patients had CD19-negative disease and 59% (30 of 52) had continued CD19 expression. In three patients, CD19 negativity was associated with myeloid transformation, two of whom had KMT2A (mixed-lineage leukemia) rearrangement. Of 129 infused patients with evaluable BCA, the probability of maintaining BCA at 6 and 12 months after infusion was 66% and 55%, respectively (Fig 2).

Of patients achieving CR, 28% (41 of 156) underwent post-CAR HSCT (median time from tisagenlecleucel to HSCT; 199 days, range, 36-565). Twenty patients (five with ongoing BCA and 15 with BCA loss) underwent HSCT while in remission after tisagenlecleucel, without intervening relapse (median time from tisagenlecleucel to HSCT; 126.5 days, range, 36-436). Survival analysis limited to patients proceeding to HSCT while in post-tisagenlecleucel remission demonstrates OS, EFS, and DOR (Data Supplement). Nineteen patients proceeded to HSCT after relapse post-tisagenlecleucel. Two patients went to HSCT with the evidence of myelodysplastic syndrome. We



Outcome	6-Month OS	1-Year OS	6-Month EFS	1-Year EFS	6-Month DOR	1-Year DOR	6-Month DBA	1-Year DBA
All patients	0.85	0.72	0.62	0.5	0.75	0.62	0.68	0.57

FIG 2. (A) OS, (B) EFS, (C) DOR, and (D) DBA outcomes of infused cohort. OS and EFS estimates in all infused, evaluable patients. DOR and DBA estimates in patients who achieved morphologic remission. DBA, duration of B-cell aplasia; DOR, duration of remission; EFS, event-free survival; OS, overall survival.

demonstrate cumulative incidence of death, RR B-ALL and/or myelodysplastic syndrome, and HSCT as competing events (Data Supplement).

Both univariate (Data Supplement) and multivariate analyses (Fig 3, Data Supplement) implicate baseline disease burden as strongly associating with outcomes. The HB cohort had decreased morphologic CR rate of 73% (95% CI, 63 to 81), as compared with 98% (95% CI, 87 to 100) in LB and 100% (95% CI, 92 to 100) in UD ($P < .0001$). OS, EFS, and DOR were lower among patients with HB at 6 and 12 months (Fig 4). Importantly, 12-month OS and EFS were 58% and 31% in HB, respectively, as compared with 85% OS and 70% EFS in LB and 95% OS and 72% EFS in UD ($P < .0001$ for OS and EFS). Analysis is limited to patients with baseline disease evaluation < 3 weeks pretisagenlecleucel, and no interval bridging therapy validates inferior HB outcomes (Data Supplement). Multivariate analysis additionally associates age 3-10 years at diagnosis ($P = .006$) and increased time from diagnosis to infusion ($P < .001$) with improved OS and expectedly associates increased prior therapy lines ($P = .022$) and relapses ($P = .005$) with decreased OS. Expanded univariate analysis is shown in the Data Supplement. Prior HSCT associates with improved OS on multivariate analysis ($P = .019$), but univariate analysis did not associate prior HSCT or CD19-directed therapy with survival outcomes, DOR, or DBA (Data Supplement). Among 35 patients who underwent leukapheresis while in remission, improved EFS is seen compared with patients collected with active disease (Data Supplement).

Safety

Among 185 patients treated with tisagenlecleucel, d28 safety was evaluable in 183 (incomplete data; n = 2).

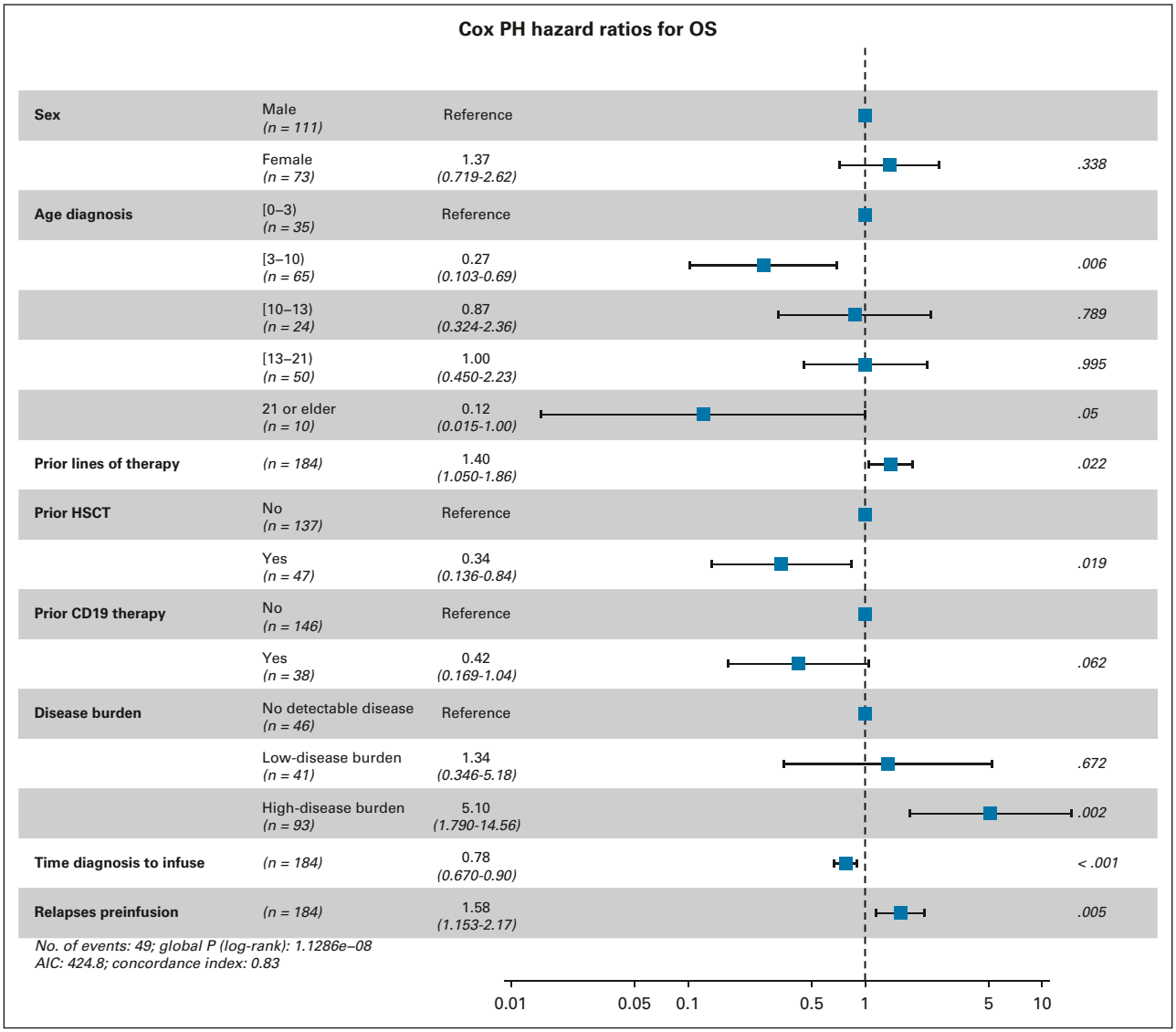


FIG 3. Association of baseline characteristics with OS in a multivariate analysis of tisagenlecleucel recipients. AIC, akaike information criterion; HSCT, hematopoietic stem cell transplantation; OS, overall survival.

Thirty-eight percent (69 of 183) and 39% (72 of 183) received lymphodepletion and tisagenlecleucel in the outpatient setting, respectively. Four patients had infusion reactions including two with anaphylaxis (Data Supplement). CRS classification as per ASTCT guidelines demonstrates overall and ≥ grade 3 CRS rates of 63% (116 of 183) and 21% (39 of 183), respectively, with one CRS-attributed death (Table 2). The median CRS onset time was 5 days (0-14 days) with a median duration of 4 days (range, 1-42). Hemophagocytic lymphohistiocytosis was reported in one patient and was managed using anakinra, dexamethasone, and etoposide.

Overall and ≥ grade 3 neurotoxicity were reported in 21% (38 of 179) and 7% (12 of 179) of patients, respectively (Table 2). One patient had cerebral edema that resolved without neurologic sequelae. A singular neurotoxicity-related death was reported with fatal cerebral hemorrhage in context of coagulopathy, CRS, and pretisagenlecleucel stroke. The median neurotoxicity onset was 6 days (range, 3-25) post-tisagenlecleucel, with a median duration of 5 days (range, 1-203 days; outlier because of prolonged facial palsy). Prior CNS3 disease did not associate with increased neurotoxicity frequency or severity (Data Supplement).

Eighty-two percent (151 of 184) of overall cohort had CAR-related hospital admissions before d28 with a median inpatient days of 14.5 (range, 1-75), and 31% (57 of 184) were admitted to the pediatric intensive care unit with a median duration of 6 days (range, 1-33). Details of tocilizumab, steroids, and vasopressor administration are reported in Table 2. Alternative therapies included anakinra (n = 3) and siltuximab (n = 1).

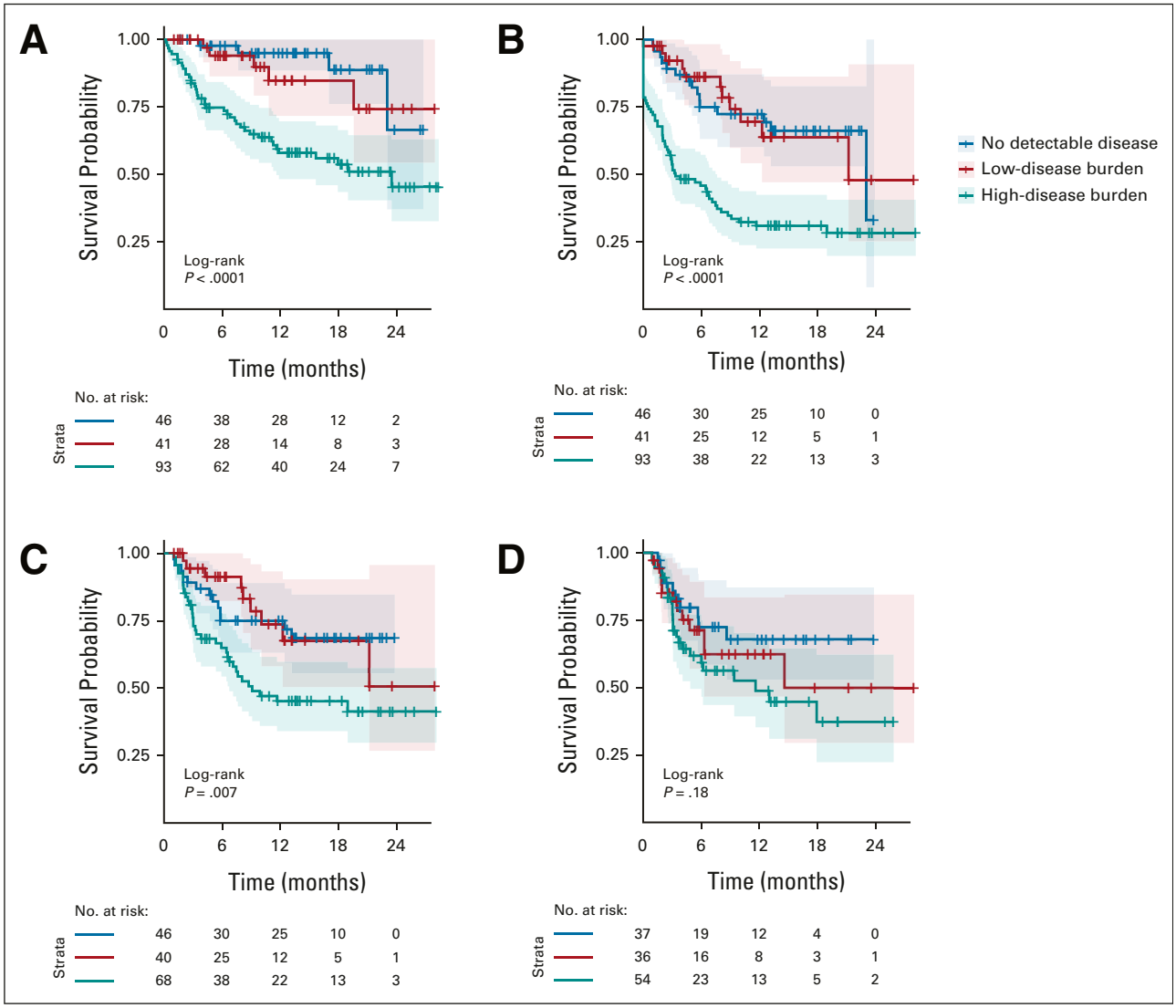


FIG 4. (A) OS, (B) EFS, (C) DOR, and (D) DBA outcomes stratified by disease burden. OS and EFS estimates in all infused patients with measurable disease burden. DOR and DBA estimates in patients who achieved morphologic remisson. (E) Disease burden stratification and day 28 CR rate. BM, bone marrow; CR, complete response; DBA, duration of B-cell aplasia; DOR, duration of remission; EFS, event-free survival; EM, extramedullary; HB, high-disease burden; LB, low-disease burden; MRD, minimal residual disease; OS, overall survival; UD, undetectable disease. (continued on following page)

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	6-month OS	1-year OS	6-month EFS	1-year EFS	6-month DOR	1-year DOR	6-month DBA	1-year DBA
No detectable disease	0.98	0.95	0.75	0.72	0.75	0.75	0.72	0.68
Low-disease burden	0.94	0.85	0.86	0.70	0.91	0.74	0.68	0.60
High-disease burden	0.75	0.58	0.46	0.31	0.65	0.45	0.60	0.45

Disease Burden Preinfusion			**No.**	**CR Rate**
HB: ≥ *5% BM lymphoblasts, detectable peripheral lymphoblasts, CNS3 and/or EM Disease*			***n = 94***	***68/93 (73%)*** *(CI, 63 to 81)*
	≥5% Lymphoblasts	No CNS or Other EM	71	54
		CNS2	2	0
		CNS3	1	0
		EM (non-CNS)	6	3
	<5% Lymphoblasts	CNS3	5	4
		EM (non-CNS)	9	7
LB: < *5% lymphoblasts, no peripheral lymphoblasts, CNS1/CNS2 disease, no detectable EM disease*			***n = 41***	***40/41 (98%)*** *(CI, 87 to 100)*
	<5% Lymphoblasts	CNS1	36	35
	<5% Lymphoblasts	CNS2	5	5
UD: *Disease undetectable by morphology or flow MRD, CNS1, no EM disease*			***n = 46***	***46/46 (100%)*** *(CI, 92 to 100)*
Disease Status Unknown			n = 4	2

FIG 4. (Continued).

Grade 4 neutropenia occurred in 118 of 175 evaluable patients, with a median duration among 94 evaluable neutropenic patients of 14 days (range, 1-76). Seven percent (13 of 175) experienced tumor lysis syndrome, and 40% (73 of 181) experienced at least one infectious complication postinfusion (median onset 68 days, range, 1-559). Fifty-one deaths occurred after tisagenlecleucel, five occurring < d28 (leukemia [n = 1], infection [n = 2], CRS [n = 1], and neurotoxicity [n = 1]). Of remaining 46 deaths, nine died without active leukemia (infection [n = 3], HSCT complications [n = 5], and cardiac [n = 1]). Nonrelapse mortality rate post-tisagenlecleucel is 7% (13 of 184).

Univariate analysis of toxicity identified disease burden and relapse versus refractory status to associate with increased CRS severity (Data Supplement). Patients with HB had increased overall CRS (79.3% [HB] *v* 51.2 [LB] and 41.3 [UD], $P < .0001$) and ≥ grade 3 CRS rates (34.7% [HB] *v* 9.8 [LB] and 0.4 [UD], $P < .0001$). Forty-three percent of patients with HB required pediatric intensive care unit–level care compared with 22% LB and 13% UD ($P < .0001$). Neurotoxicity did not significantly differ between subgroups (Data Supplement). Univariate outcome analysis associated ≥ grade 3 CRS with decreased OS and EFS ($P < .0001$; Data Supplement).

DISCUSSION

Multi-institutional, retrospective data on 185 CAYA patients infused with commercial tisagenlecleucel demonstrate overall comparable response, OS, and EFS rates with previous reported series.[9,10] However, increased disease burden associates with inferior tisagenlecleucel outcomes. It remains unclear if disease burden is a surrogate of distinct biology driving inferior outcomes or this is a modifiable factor that is responsive to debulking before CAR infusion.

Although ELIANA required > 5% BM lymphoblasts with a median of 75% at enrollment,[9] the US Food and Drug Administration–approved indication for tisagenlecleucel does not require a threshold disease burden. In our series, 48% of infused patients had LB (< 5% BM lymphoblasts, no CNS3, or other EM) or UD disease at the last evaluation before CAR. Disease burden on ELIANA was assessed at enrollment and may shift during manufacturing or with bridging chemotherapy. Direct comparisons across studies are, therefore, inherently challenged; however, our study likely represents a cohort with an overall lower-disease burden than ELIANA.

Impact of disease burden was previously described in adults with ALL receiving CD19-targeting (19-28z) CAR T cells where patients with LB or UD disease had longer EFS and OS, as compared with patients with ≥ 5% BM lymphoblasts or EM disease.[19] Pediatric data using the same construct support that minimal disease burden positively affect response.[12] In the commercial setting, the Center for International Blood and Marrow Transplant Research described comparable tisagenlecleucel efficacy with previous pivotal trials, across pediatric and adult leukemia and lymphoma.[20] Similar to our data set, high

TABLE 2. Summary of Safety Using Commercial Tisagenlecleucel

Toxicity	No. (%)
CRS (N = 183)	
None	67 (37)
Any; grade 1, 2, 3, 4, or 5	116 (63); 45, 32, 19, 19, 1
Neurotoxicity (n = 179)	
None	141 (79)
Any; grade 1, 2, 3, 4, or 5	38 (21); 19, 7, 8, 3, 1
Cerebral edema	1 (0.6)
Cerebral hemorrhage	1 (0.6)
Treatment	
Tocilizumab	
Yes, median doses (range)	46 (27); 2 (1-5)
No	127 (73)
Steroids	
Yes, median days (range)	26 (15); 7 (0-31)
No	142 (85)
Vasopressor	
Yes	31 (18)
No	146 (82)
Tumor lysis syndrome	
Yes	13 (7)
No	162 (93)
Grade 4 neutropenia persistent > day 28 (analysis limited to patients with CR and evaluable counts, N = 147)	
Yes	23 (16)
No	124 (84)
Infections	
Patients	73 (40)
Infections/patient; median (range)	1 (1-5)
PICU stay	
Yes, duration (days); median (range)	57 (31); 6 (1-33)
No	125 (68)

Abbreviations: CR, complete response; CRS, cytokine release syndrome, PICU, pediatric intensive care unit.

response rates were seen in patients entering CAR without detectable disease. However, survival outcomes were not stratified across disease burden. Real-world study of axicabtagene ciloleucel (Yescarta) in adult B-cell lymphoma identifies increased lactate dehydrogenase, a biomarker correlating with disease bulk, as an independent variable of poor response.[21]

Conversely, previous work in pediatrics supports that low absolute numbers of CD19-expressing target cells (both healthy and malignant B cells) at the time of CAR infusion associate with shortened CAR T-cell engraftment.[10] Although we found 64% of patients with LB or UD disease maintained BCA for at least 1 year, we did not assess normal B-cell numbers preinfusion.

Decreased toxicity in our cohort, as compared with ELIANA, may relate to lower-disease burden or an evolving threshold for intervention. Similar to previous work associating tumor burden with post-CAR toxicity in pediatric ALL,[8] we report increased CRS incidence and severity in patients infused with HB. Thirty-nine percent of our cohort were infused as outpatients. The low rate of infusion-related toxicity, lag between tisagenlecleucel-infusion and CRS-onset (median; 5 days), and experience that CRS starts with low-grade symptoms support outpatient tisagenlecleucel infusion as a safe practice.

Interestingly, compared with ELIANA where 15 of 16 patients with evaluable antigen status relapsed with CD19-negative disease, we report that majority of relapses have preserved CD19 surface expression in this cohort (59% CD19-positive *v* 41% CD19-negative). Whether this finding relates to differences in tisagenlecleucel expansion and persistence because of lower disease/CD19 antigen burden, or alternative factors, including varying thresholds for defining antigen downregulation, warrants further study. Intriguingly, this analysis did not find patients with lower-disease burden to have decreased DBA.

Limitations of this study derive from the retrospective nature and heterogeneity of reporting across centers and evolving definitions of disease response and relapse. Additionally, evolving toxicity grading systems were adopted by participating institutions at different times. Although CRS was regraded according to ASTCT, data were not available to regrade neurotoxicity. Timing of the last disease burden assessment before tisagenlecleucel varied across centers, with possible changes in burden during the bridging/manufacturing window. If disease burden changed before infusion, it would tend to blunt the impact of disease burden on outcomes observed in our analysis. That disease burden remained highly prognostic suggests a true effect. Nonetheless, further study to quantify the impact of disease burden assessed immediately pretisagenlecleucel will be important. Finally, we are unable to assess the impact of planned consolidative HSCT after tisagenlecleucel given the rarity with which this was undertaken in this study cohort.

In conclusion, we report the feasibility of commercial tisagenlecleucel delivery, with comparable overall response and survival outcomes with the landmark ELIANA trial and decreased toxicity and antigen downregulation in context of lower overall disease burden. Importantly, disease burden associates with response, survival, and toxicity, and patients with HB emerge as a distinct high-risk population who may benefit from further interventional strategies to optimize CAR-mediated outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report

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