ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

ABSTRACT

BACKGROUND

In a single-center phase 1–2a study, the anti-CD19 chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel produced high rates of complete remission and was associated with serious but mainly reversible toxic effects in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).

METHODS

We conducted a phase 2, single-cohort, 25-center, global study of tisagenlecleucel in pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL. The primary end point was the overall remission rate (the rate of complete remission or complete remission with incomplete hematologic recovery) within 3 months.

RESULTS

For this planned analysis, 75 patients received an infusion of tisagenlecleucel and could be evaluated for efficacy. The overall remission rate within 3 months was 81%, with all patients who had a response to treatment found to be negative for minimal residual disease, as assessed by means of flow cytometry. The rates of event-free survival and overall survival were 73% (95% confidence interval [CI], 60 to 82) and 90% (95% CI, 81 to 95), respectively, at 6 months and 50% (95% CI, 35 to 64) and 76% (95% CI, 63 to 86) at 12 months. The median duration of remission was not reached. Persistence of tisagenlecleucel in the blood was observed for as long as 20 months. Grade 3 or 4 adverse events that were suspected to be related to tisagenlecleucel occurred in 73% of patients. The cytokine release syndrome occurred in 77% of patients, 48% of whom received tocilizumab. Neurologic events occurred in 40% of patients and were managed with supportive care, and no cerebral edema was reported.

CONCLUSIONS

In this global study of CAR T-cell therapy, a single infusion of tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects. (Funded by Novartis Pharmaceuticals; ClinicalTrials.gov number, NCT02435849.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Maude at 3012 Colket Translational Research Bldg., 3501 Civic Center Blvd., Philadelphia, PA 19104, or at maude@email.chop.edu.

Drs. Pulsipher and Grupp contributed equally to this article.

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Tisagenlecleucel (formerly CTL019), an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, is under investigation in patients with relapsed or refractory B-cell cancers, including B-cell acute lymphoblastic leukemia (ALL). Results from a single-center phase 1–2a study of tisagenlecleucel involving 60 children and young adults with relapsed or refractory B-cell ALL that was conducted at the Children's Hospital of Philadelphia and the University of Pennsylvania showed a rate of complete remission of 93%.[1] The cytokine release syndrome, a common adverse event associated with CAR T-cell therapies, occurred in 88% of patients and was effectively managed with supportive measures and anticytokine therapy, including the interleukin-6 receptor antagonist tocilizumab.[1] Long-term disease control without additional therapy and with persistence of tisagenlecleucel for up to 4 years has been observed.[1,2]

On the basis of these results, a phase 2 pivotal, multisite study of tisagenlecleucel was initiated. In this nonrandomized study of CAR T-cell therapy, we used a global supply chain and included 25 study sites in 11 countries across North America, Europe, Asia, and Australia. Here we report the results of a planned analysis of data from the study, including analyses of the efficacy, safety, and cellular kinetics of tisagenlecleucel in 75 patients with at least 3 months of follow-up.

Methods

Study Design

We conducted a single-cohort, phase 2, multicenter, global study of tisagenlecleucel in children and young adults with relapsed or refractory B-cell ALL. To be eligible for participation in the study, patients had to be at least 3 years of age at screening and no older than 21 years of age at diagnosis and to have at least 5% lymphoblasts in bone marrow at screening. Patients who had previously received anti-CD19 therapy were excluded (see the Methods section of the Supplementary Appendix, available with the full text of this article at NEJM.org).

Tisagenlecleucel was generated ex vivo with the use of autologous T cells transduced with a lentiviral vector to express a CAR containing a CD3-zeta domain to provide a T-cell activation signal and a 4-1BB (CD137) domain to provide a costimulatory signal.[3]

The study was sponsored and designed by Novartis Pharmaceuticals and was approved by the institutional review board at each participating institution. Patients or their guardians provided written informed consent or assent. Data were analyzed and interpreted by the sponsor in collaboration with the authors, and all the authors reviewed the manuscript and vouch for accuracy and completeness of the data and analyses and for adherence of the study to the protocol, available at NEJM.org. The first author wrote the first draft of the manuscript in conjunction with authors from Novartis. All the authors contributed to the writing of the manuscript and approved the final version for submission. Medical editorial assistance was provided by editors whose work was financially supported by Novartis.

End Points

The primary end point was an overall remission rate higher than 20% (the null hypothesis). The overall remission rate was defined as the rate of a best overall response of either complete remission or complete remission with incomplete hematologic recovery within 3 months, as assessed by an independent review committee on the basis of the results of laboratory testing of blood, bone marrow, and cerebrospinal fluid (CSF), as well as physical examination. Responses were required to be maintained for at least 28 days (see the Methods section in the Supplementary Appendix). Secondary end points included the rate of complete remission or complete remission with incomplete hematologic recovery with undetectable minimal residual disease (<0.01%) assessed by means of central multiparameter flow cytometry, the duration of remission, event-free survival (i.e., the time from infusion to the earliest of the following events: no response, relapse before response was maintained for at least 28 days, or relapse after having complete remission or complete remission with incomplete hematologic recovery), overall survival, cellular kinetics, and safety. Additional details regarding the secondary end points are provided in the Supplementary Appendix.

Statistical Analysis

The primary end point was evaluated in the full analysis set. We determined that a sample of 76 patients receiving a tisagenlecleucel infusion would provide more than 95% power to reject

the null hypothesis of an overall remission rate of 20% against the alternative hypothesis of an overall remission rate of 45% or higher at an overall one-sided significance level of 2.5%.

An interim analysis was planned after the first 50 patients who received a tisagenlecleucel infusion had completed 3 months of follow-up or discontinued participation in the study. The results with regard to the primary end point were considered to be significant in the interim analysis if the one-sided P value was lower than 0.0057. Key secondary end points were tested sequentially (after the primary end point was significant) to control the overall alpha.

The results with regard to overall remission rate, response duration, event-free survival, overall survival, cellular kinetics, and safety that are presented in this report are from an updated analysis that included 75 patients who received tisagenlecleucel and had completed 3 months of follow-up or discontinued the study at an earlier point. For the time-to-event analyses, Kaplan–Meier curves were used to estimate survival distributions after infusion. All statistical tests were performed with the use of SAS software, version 9.4 (SAS Institute). Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

Between April 8, 2015, and the data cutoff on April 25, 2017, a total of 107 patients were screened, and 92 were enrolled (Fig. 1). A total of 75 patients received an infusion of tisagenlecleucel, with a median time from enrollment to infusion of 45 days (range, 30 to 105). The median duration of follow-up among patients who received a tisagenlecleucel infusion was 13.1 months. At enrollment, patients who received tisagenlecleucel had a median age of 11 years (range, 3 to 23), a median of 3 previous therapies (range, 1 to 8), and a median marrow blast percentage of 74% (range, 5 to 99); 46 patients (61%) had undergone previous allogeneic hematopoietic stem-cell transplantation (Table S1 in the Supplementary Appendix).

Before tisagenlecleucel infusion, 72 of 75 patients (96%) received lymphodepleting chemo-

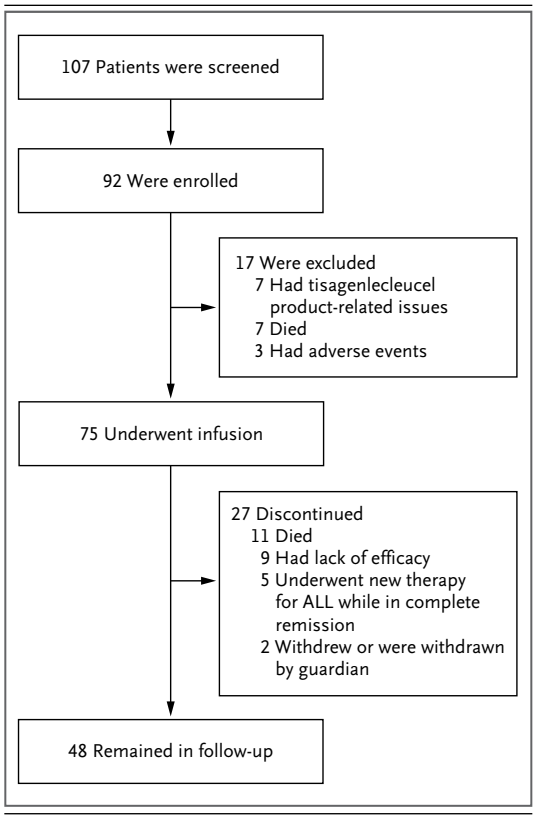

Figure 1. Screening, Enrollment, Treatment, and Follow-up.

The first patient's first visit occurred on April 8, 2015. The median time from tisagenlecleucel infusion to data cutoff was 13.1 months. The reasons for patients not enrolling in the study after screening included not meeting the inclusion criteria or meeting the exclusion criteria (11 patients, including <5% blasts in the bone marrow in 8 patients), death before acceptance of the apheresis sample at the manufacturing facility (2 patients; 1 who died from pulmonary hemorrhage and 1 who died from multiorgan failure), physician decision (1), and apheresis-related issue (1). All patients who completed screening and whose apheresis product was received and accepted by the manufacturing facility were enrolled in the study. Of the 75 patients who received an infusion, 65 (87%) received bridging chemotherapy between enrollment and infusion, and 72 (96%) received lymphodepleting chemotherapy (fludarabine–cyclophosphamide [71 patients] or cytarabine–etoposide [1]). Seventeen enrolled patients did not receive a tisagenlecleucel infusion because of product-related issues (7 patients), death (7 patients; 4 from disease progression and 1 each from sepsis, respiratory failure, and fungemia), and adverse events (3 patients; 1 each from graft-versus-host disease, systemic mycosis, and fungal pneumonia). Tisagenlecleucel product-related issues included an inability to manufacture as a result of poor cell growth for 6 patients and a technical issue unrelated to cell growth for 1 patient. Patients who received the infusion but discontinued follow-up were followed for survival. At the time of data cutoff, 27 patients had discontinued follow-up owing to death (11 patients; 7 from disease progression and 1 each from encephalitis, cerebral hemorrhage, systemic mycosis, and hepatobiliary disorders related to allogeneic hematopoietic stem-cell transplantation), lack of efficacy (9 patients; nonresponse or relapse), new therapy while in complete remission (5), and patient or guardian decision (2); 48 patients remained in follow-up. ALL denotes acute lymphoblastic leukemia.

therapy, which was not given at investigator discretion if a patient had leukopenia. Patients received a median weight-adjusted dose of 3.1×10^6 transduced viable T cells per kilogram of body weight (range, 0.2×10^6 to 5.4×10^6 cells per kilogram); the median total dose of transduced viable T cells was 1.0×10^8 (range, 0.03×10^8 to 2.6×10^8 cells) (Table S2 in the Supplementary Appendix).

EFFICACY

In the interim analysis, which included 50 patients, the primary end point was met, with an overall remission rate of 82% (95% confidence interval [CI], 69 to 91; P<0.001); the results with regard to all key secondary end points were also significant.[4] In this updated analysis involving 75 patients who received a tisagenlecleucel infusion and had at least 3 months of follow-up, the overall remission rate was 81% (95% CI, 71 to 89); 45 patients (60%) had complete remission, and 16 (21%) had complete remission with incomplete hematologic recovery. All patients who had a best overall response of complete remission with or without complete hematologic recovery were negative for minimal residual disease; 95% (58 of 61) of these patients were negative by day 28. In an intention-to-treat analysis of the full enrolled population (92 patients), which included patients who discontinued participation in the study before tisagenlecleucel infusion, the overall remission rate was 66% (95% CI, 56 to 76) (Table S3 in the Supplementary Appendix). In subgroup analyses that included patients with or without previous transplantation, with high-risk genomic lesions, or with Down's syndrome, the overall remission rate ranged from 79% to 83% (Fig. S1 in the Supplementary Appendix).

Among the 61 patients with complete remission with or without complete hematologic recovery, the median response duration was not reached (Fig. 2A). The rate of relapse-free survival among patients with a response to treatment was 80% (95% CI, 65 to 89) at 6 months and 59% (95% CI, 41 to 73) at 12 months. Among patients with complete remission, 17 had a relapse before receiving additional anticancer therapy. Relapse also occurred in 3 patients who proceeded to receive new cancer therapy for the emergence of minimal residual disease or loss of tisagenlecleucel persistence and in 2 patients who had already been classified as not having a response to treatment because remission was not maintained for at least 28 days. No patients were found to have relapses in the central nervous system (CNS) during primary follow-up; 1 CNS relapse was reported after new anticancer therapy. Characterization of CD19 status at the time of relapse showed that 1 patient had a CD19+ recurrence and 15 patients had CD19− (3 with concomitant CD19+ blasts); 6 patients had unknown CD19 status.

The rate of event-free survival was 73% (95% CI, 60 to 82) at 6 months and 50% (95% CI, 35 to 64) at 12 months (Fig. 2B); median event-free survival was not reached. Eight patients underwent allogeneic hematopoietic stem-cell transplantation while in remission, including 2 patients with minimal residual disease–positive bone marrow and 2 with B-cell recovery within 6 months after infusion. All 8 patients were alive at the time of manuscript submission — 4 with no relapse and 4 with unknown disease status. The rate of overall survival among the 75 patients who received tisagenlecleucel was 90% (95% CI, 81 to 95) at 6 months after infusion and 76% (95% CI, 63 to 86) at 12 months after infusion (Fig. 2B, and Fig. S2 in the Supplementary Appendix).

TISAGENLECLEUCEL EXPANSION AND PERSISTENCE

Tisagenlecleucel transgene was detected in peripheral blood by means of qualitative polymerase chain reaction.[5] Among the 60 patients with a response at day 28 who could be evaluated for cellular kinetics, the median time to maximum expansion (T_{max}) was 10 days (range, 5.7 to 28), whereas 6 patients with no response had a T_{max} of 20 days (range, 13 to 63) (Table S4 in the Supplementary Appendix). Nine patients who could not be evaluated for response were not included in the analysis. Expansion, measured as the geometric mean of the area under the concentration–time curve in peripheral blood from time 0 to day 28 (expressed as copies per microgram of DNA times days), was 315,000 in patients with a response and 301,000 in patients without a response (Table S4 in the Supplementary Appendix). The median duration of persistence of tisagenlecleucel in blood was 168 days (range, 20 to 617 days; 60 patients) at data cutoff. Across the wide range of doses infused, no relationship between dose and expansion was observed ($r^2<0.001$) (Fig. S3 in the Supplementary Appendix), and clinical responses were observed across the entire dose range.

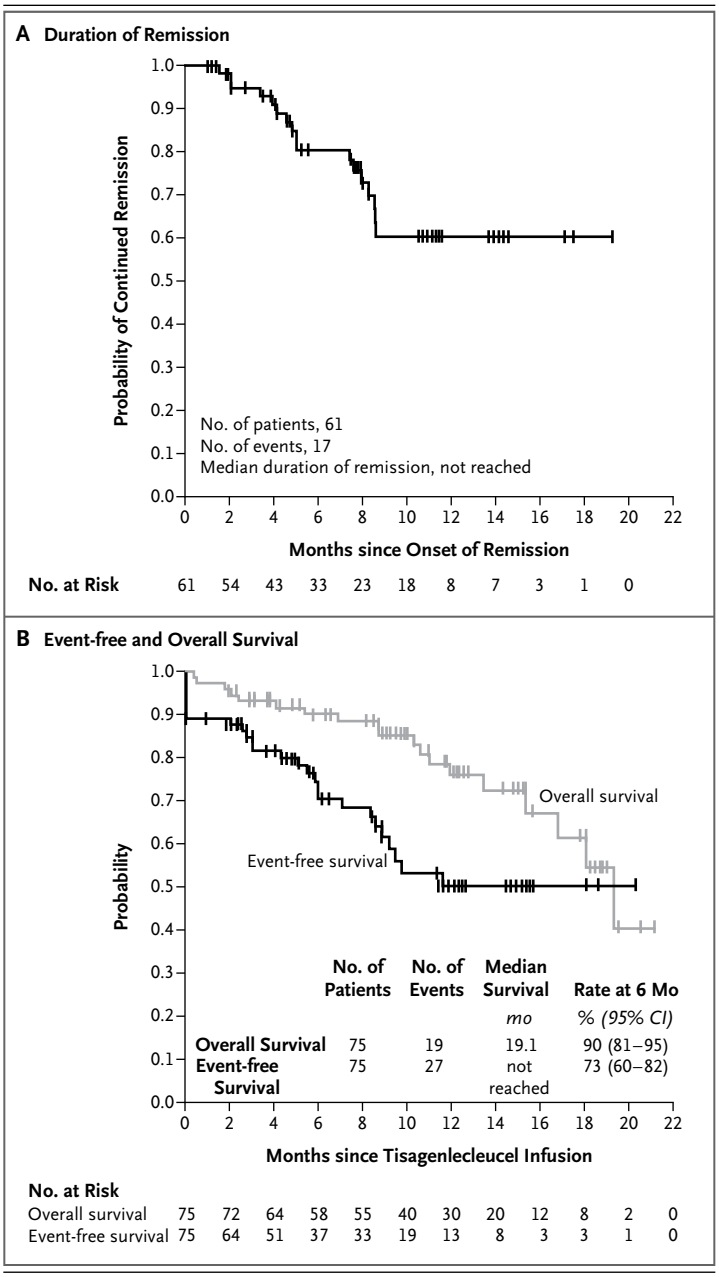

Figure 2. Duration of Remission, Event-free Survival, and Overall Survival.

Panel A shows the duration of remission, defined as the time to relapse after the onset of remission, in the 61 patients who had a best overall response of either complete remission or complete remission with incomplete hematologic recovery. Panel B shows event-free survival among the 75 patients who received an infusion, defined as the time from tisagenlecleucel infusion to the earliest of the following events: no response (8 patients), relapse before response was maintained for at least 28 days (2), or relapse after having complete remission or complete remission with incomplete hematologic recovery (17). A total of 32 patients had still not had an event at the time of data cutoff. Data for 16 more patients were censored for event-free survival — 8 patients for allogeneic stem-cell transplantation during remission, 7 patients for new cancer therapy other than stem-cell transplantation during remission (4 received humanized anti-CD19 CAR T cells, 1 received ponatinib, 1 received vincristine sulfate and blinatumomab, and 1 received antithymocyte globulin), and 1 patient for lack of adequate assessment. Ten patients were followed for relapse after new therapy, 4 of whom had a relapse or died. Panel B also shows overall survival among the 75 patients who received an infusion from the date of tisagenlecleucel infusion to the date of death from any cause. Nineteen patients died after tisagenlecleucel infusion, and 56 patients had their data censored at the time of the last follow-up. Tick marks indicate the time of censoring.

B-CELL APLASIA

All patients with a response to treatment had B-cell aplasia, and most patients in the study received immunoglobulin replacement in accordance with local practice. The median time to B-cell recovery was not reached (Fig. S4 in the Supplementary Appendix). The probability of maintenance of B-cell aplasia at 6 months after infusion was 83% (95% CI, 69 to 91).

CYTOKINE RESPONSE

Among the 75 patients who received tisagenlecleucel, transient increases in serum interleukin-6, interferon gamma, and ferritin levels occurred during the cytokine release syndrome after infusion; these increases tended to be more pronounced in patients with grade 4 cytokine release syndrome than in patients with lower grades (Fig. S5 in the Supplementary Appendix). Similar trends were observed in the levels of other cytokines, including interleukin-10, interleukin-12p70, interleukin-1β, interleukin-2, interleukin-4, interleukin-8, and tumor necrosis factor α. A transient increase in the C-reactive protein level was observed in most patients, but with large variability.

SAFETY

The safety analysis set included all 75 patients who received an infusion of tisagenlecleucel; the median time from infusion to data cutoff was 13.1 months (range, 2.1 to 23.5). Eighteen patients (24%) received their infusions in an outpatient setting. All patients had at least one adverse event during the study; 71 of 75 patients (95%)

Table 1. Overall Safety of Tisagenlecleucel.

Event	Any Time (N=75)	≤8 Wk after Infusion (N=75)	>8 Wk to 1 Yr after Infusion (N=70)
	number of patients (percent)		
Adverse event of any grade	75 (100)	74 (99)	65 (93)
Suspected to be related to tisagenlecleucel	71 (95)	69 (92)	30 (43)
Grade 3 or 4 adverse event	66 (88)	62 (83)	31 (44)
Suspected to be related to tisagenlecleucel	55 (73)	52 (69)	12 (17)

had an adverse event that was suspected by the investigators to be related to tisagenlecleucel (Table 1). The most common nonhematologic adverse events of any grade at any time after infusion were the cytokine release syndrome (77%), pyrexia (40%), decreased appetite (39%), febrile neutropenia (36%), and headache (36%) (Tables S6 and S7 in the Supplementary Appendix). Within 8 weeks after infusion, febrile neutropenia occurred in 35% of the patients, and grade 3 or 4 neutropenia with a body temperature higher than 38.3°C occurred in 46 of 75 patients (61%). Fever, neutropenia, and the cytokine release syndrome often occurred concurrently after lymphodepleting chemotherapy and tisagenlecleucel infusion; differences in reporting may reflect differential attribution of fever to the cytokine release syndrome rather than to neutropenia.

A total of 66 of 75 patients (88%) had a grade 3 or 4 adverse event; 55 of 75 patients (73%) had a grade 3 or 4 tisagenlecleucel-related adverse event (Table 1). Within 8 weeks after infusion, 52 of 75 patients (69%) had a grade 3 or 4 tisagenlecleucel-related adverse event; during the period from 8 weeks to 1 year after infusion, the incidence decreased to 12 of the 70 patients for whom follow-up data were available (17%) (Table 2). Adverse events of special interest included the cytokine release syndrome, cytopenias not resolved by day 28, infections, neurologic events, and the tumor lysis syndrome; 67 of 75 patients (89%) had an adverse event of special interest within 8 weeks after infusion (Table 3). The cytokine release syndrome occurred in 58 of 75 patients (77%); the median time to onset was 3 days (range, 1 to 22), and the median duration was 8 days (range, 1 to 36). A total of 35 of 75 patients (47%) were admitted to the intensive care unit (ICU) for management of the cytokine release syndrome, with a median stay of 7 days (range, 1 to 34). Nineteen patients (25%) were treated with high-dose vasopressors, 33 (44%) received oxygen supplementation, 10 (13%) received mechanical ventilation, 7 (9%) underwent dialysis, and 28 (37%) received tocilizumab for management of the cytokine release syndrome.[6]

Neurologic events occurred in 30 of 75 patients (40%) within 8 weeks after infusion. Ten patients (13%) had grade 3 neurologic events; no grade 4 events or cerebral edema were reported. The most common neurologic events of any grade were encephalopathy (11%), confusional state (9%), delirium (9%), tremor (8%), agitation (7%), and somnolence (7%); 1 patient had a seizure (grade 3). The majority of neurologic events occurred during the cytokine release syndrome or shortly after its resolution. Severe neurologic events occurred more frequently in patients with higher-grade cytokine release syndrome (Table S7 in the Supplementary Appendix); grade 3 neurologic events occurred more frequently in patients with grade 4 cytokine release syndrome than among those with grade 0 through 3 (32% [6 of 19] vs. 7% [4 of 56]; 95% CI for the difference, –1 to 50 percentage points). Among grade 3 neurologic episodes that resolved, 50% resolved within 10 days, and 75% resolved within 18 days. Four grade 3 neurologic episodes were unresolved in 3 patients at the time of discontinuation for no response (1 patient) or at the time of death (1 death due to leukemia progression and 1 due to encephalitis), 2 of which were thought to be related to tisagenlecleucel (1 each of encephalopathy and delirium). Neurologic events were managed with supportive care after ruling out other potential causes of the symptoms.

Table 2. Grade 3 or 4 Adverse Events Suspected to Be Related to Tisagenlecleucel That Occurred in at Least 5% of Patients.

Event	≤8 Wk after Infusion (N=75)		>8 Wk to 1 Yr after Infusion (N=70)	
	Grade 3	Grade 4	Grade 3	Grade 4
	number of patients (percent)			
Any grade 3 or 4 adverse event	19 (25)	33 (44)	8 (11)	4 (6)
Cytokine release syndrome	16 (21)	19 (25)	—	—
Hypotension	7 (9)	6 (8)	—	—
Decrease in lymphocyte count	5 (7)	4 (5)	1 (1)	—
Hypoxia	5 (7)	3 (4)	—	—
Increase in blood bilirubin	8 (11)	—	—	—
Increase in aspartate aminotransferase	5 (7)	2 (3)	—	—
Pyrexia	5 (7)	2 (3)	—	—
Decrease in neutrophil count	1 (1)	6 (8)	1 (1)	1 (1)
Decrease in white-cell count	—	7 (9)	—	—
Decrease in platelet count	3 (4)	4 (5)	—	—
Decrease in appetite	6 (8)	1 (1)	—	—
Acute kidney injury	3 (4)	3 (4)	—	—
Hypophosphatemia	5 (7)	1 (1)	—	—
Hypokalemia	6 (8)	—	—	—
Pulmonary edema	4 (5)	1 (1)	—	—
Thrombocytopenia	1 (1)	4 (5)	—	1 (1)
Encephalopathy	4 (5)	—	—	—
Increase in alanine aminotransferase	4 (5)	—	—	—
Fluid overload	4 (5)	—	—	—

A total of 31 of 75 patients (41%) had grade 3 or 4 decreased platelet counts that had not resolved by day 28. Of those 31 patients, 22 had resolution to grade 2 or lower by the last assessment, and 9 did not. By month 3, the Kaplan–Meier estimate of the percentage of patients with resolution to grade 2 or lower was 73%. A grade 3 or 4 decreased neutrophil count that had not resolved by day 28 was reported in 40 of 75 patients (53%). Of those 40 patients, 32 had resolution to grade 2 or lower by the last assessment, and 8 did not; the Kaplan–Meier estimate of the percentage of patients who had resolution to grade 2 or lower by month 3 was 66%. Eighteen of these 40 patients (45%) had grade 3 or 4 infections. In rare cases, prolonged grade 3 or 4 neutropenia before and after tisagenlecleucel infusion was associated with infections that were severe (grade 3 human herpesvirus 6 [HHV-6] encephalitis) or fatal (encephalitis and systemic mycosis).

Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

Type of Event	Any Grade (N=75)	Grade 3 (N=75)	Grade 4 (N=75)
	number of patients (percent)		
Any adverse event of special interest	67 (89)	26 (35)	30 (40)
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Neurologic event	30 (40)	10 (13)	0
Infection	32 (43)	16 (21)	2 (3)
Febrile neutropenia	26 (35)	24 (32)	2 (3)
Cytopenia not resolved by day 28	28 (37)	12 (16)	12 (16)
Tumor lysis syndrome	3 (4)	3 (4)	0

* The criteria for defining adverse events of special interest were based on experience from ongoing clinical studies. The cytokine release syndrome includes the Medical Dictionary for Regulatory Activities preferred terms "cytokine release syndrome," "cytokine storm," "shock," "macrophage activation," and "hemophagocytic lymphohistiocytosis." Neurologic events include the standardized Medical Dictionary for Regulatory Activities query terms "noninfectious encephalopathy" and "delirium."

Nineteen deaths occurred after tisagenlecleucel infusion. Within 30 days after infusion, 1 patient died from cerebral hemorrhage in the context of coagulopathy and resolving cytokine release syndrome (15 days after infusion), and 1 patient died from progressive B-cell ALL. More than 30 days after infusion, 17 patients died; the causes of death were B-cell ALL relapse or progression (12 patients), HHV-6–positive encephalitis in association with prolonged neutropenia and lymphopenia (1), systemic mycosis in association with prolonged neutropenia (1), and unknown causes (1); in 2 patients, death occurred after new therapies for B-cell ALL (1 from pneumonia and 1 from hepatobiliary disease).

DISCUSSION

In this global, multicenter, pivotal study of CAR T-cell therapy, high response rates were shown in children and young adults with relapsed or refractory B-cell ALL, 61% of whom had had a relapse after allogeneic hematopoietic stem-cell transplantation. Effective distribution of tisagenlecleucel across four continents with the use of a global supply chain was shown to be feasible and resulted in efficacy and safety similar to those observed in the previous, single-center study.[1]

This updated analysis showed an overall remission rate of 81% among 75 patients with at least 3 months of follow-up after a single infusion of tisagenlecleucel. The remissions were durable, with a 6-month relapse-free survival rate of 80%. The durability of the clinical response was associated with persistence of tisagenlecleucel in peripheral blood and with persistent B-cell aplasia.

The treatment of patients who have relapsed or refractory B-cell ALL after failure of two regimens is challenging. The rate of minimal residual disease–negative overall remission of 81% and the 6-month overall survival rate of 90% found in this study of tisagenlecleucel compare favorably with the rates achieved with Food and Drug Administration–approved agents for relapsed B-cell ALL. A pivotal phase 2 study of clofarabine involving 61 pediatric patients with relapsed or refractory ALL showed a response rate of 20%, a median response duration of 29 weeks (range, 1 to 48), and a median overall survival of 13 weeks (range, 1 to 89).[7] In a study of the CD19–CD3 bispecific antibody blinatumomab, complete remission occurred in 27 of the 70 pediatric patients (39%) with relapsed or refractory B-cell ALL within the first two cycles of blinatumomab treatment, with a rate of negativity for minimal residual disease of 20% and a median overall survival of 7.5 months.[8]

High rates of complete remission have also been found in pediatric and adult patients with relapsed or refractory ALL treated with other anti-CD19 CAR T-cell therapies, and U.S. multicenter phase 1–2 studies of the CAR T-cell therapy KTE-C19 have been initiated in pediatric and adult patients with relapsed or refractory ALL.[9-14] One key difference between CAR designs is the costimulatory domain; tisagenlecleucel contains a 4-1BB domain, which has been suggested to improve the persistence of CAR T cells through amelioration of T-cell exhaustion.[15] In a phase 1 study of KTE-C19, which contains a CD28 domain, involving 21 children and young adults, CAR T cells were not detected beyond 68 days; therefore, KTE-C19 has been used as a bridge to allogeneic transplantation for most patients who receive it.[13] In an updated analysis involving 38 patients, all but 1 patient in sustained remission proceeded to undergo allogeneic transplantation, and median leukemia-free survival was 17.7 months.[16] The anti-CD19 CAR T-cell therapy JCAR017, which contains a 4-1BB costimulatory domain, was recently shown to result in a median expected duration of B-cell aplasia of 3 months in a cohort of 42 pediatric and young adult patients with ALL and was detected at 6 months in patients with relapsed or refractory non-Hodgkin's lymphoma who had a response to treatment.[17,18] In an analysis involving 29 adult patients with ALL who were treated with JCAR017, of whom 27 had complete remission, 8 of the 13 in ongoing remission underwent subsequent allogeneic transplantation.[19] In the present study, the median persistence of tisagenlecleucel was 168 days at data cutoff, with ongoing persistence for as long as 20 months and relapse-free survival rates of 80% at 6 months and 59% at 12 months, with only 9% of patients proceeding to undergo allogeneic transplantation.

Previous studies showing promising results with anti-CD19 CAR T-cell therapies in the treatment of relapsed and refractory B-cell ALL were single-center studies, with manufacture occurring on site; therefore, the reproducibility and

feasibility of central manufacture in a global, multicenter setting remained uncertain. The toxicity and efficacy of tisagenlecleucel in this global, multicenter study were consistent with those in the single-center study, and the feasibility of a global supply chain was demonstrated.[1,4] Because this study used cryopreserved leukapheresis product (see the Methods section in the Supplementary Appendix), it did not require fresh product and an open manufacture slot for enrollment. Training in the management of toxic effects and data collection included implementation of a grading scale for the cytokine release syndrome that was developed at the University of Pennsylvania and Children's Hospital of Philadelphia, as well as a defined cytokine release syndrome management algorithm (Table S9 in the Supplementary Appendix).[20] Tisagenlecleucel was administered as a single infusion, and most toxic effects were observed only during the first 8 weeks after infusion. The product could be administered in the outpatient setting. In some cases, centers would initially elect to administer infusions to inpatients and then change to outpatient administration after they had gained more experience. Patients who were treated in the outpatient setting were admitted for fever. The median time from the onset of the cytokine release syndrome to grade 3 or 4 levels was 3 days. Although nearly half the patients received care in an ICU, the criteria for admission to the ICU varied widely across institutions. A total of 25% of patients were treated with high-dose vasopressors, a treatment commonly administered in intensive care settings.

Neurologic adverse events, which have been observed with anti-CD19 CAR T-cell therapies and blinatumomab,[8-10,21] occurred in our study. Most neurologic adverse events were transient, did not include cerebral edema, and appeared to be more frequent in patients with higher-grade cytokine release syndrome.

Ongoing tisagenlecleucel persistence was observed more than 1 year after infusion in patients with a treatment response. Across a 2-log tisagenlecleucel dose range, multi-log expansion occurred, and no relationship between infusion dose and expansion was found. This finding indicates that patients can be effectively treated with tisagenlecleucel across a wide dose range without an apparent effect on expansion and response.

In conclusion, tisagenlecleucel produced high remission rates and durable remissions without additional therapy in high-risk pediatric and young adult patients with relapsed or refractory B-cell ALL. The risks associated with tisagenlecleucel are substantial, leading to ICU-level care in some cases, but were mitigated in most patients with supportive measures and cytokine blockade.

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APPENDIX

The authors' full names and academic degrees are as follows: Shannon L. Maude, M.D., Ph.D., Theodore W. Laetsch, M.D., Jochen Buechner, M.D., Ph.D., Susana Rives, M.D., Ph.D., Michael Boyer, M.D., Henrique Bittencourt, M.D., Ph.D., Peter Bader, M.D., Michael R. Verneris, M.D., Heather E. Stefanski, M.D., Ph.D., Gary D. Myers, M.D., Muna Qayed, M.D., Barbara De Moerloose, M.D., Ph.D., Hidefumi Hiramatsu, M.D., Ph.D., Krysta Schlis, M.D., Kara L. Davis, D.O., Paul L. Martin, M.D., Ph.D., Eneida R. Nemecek, M.D., Gregory A. Yanik, M.D., Christina Peters, M.D., Andre Baruchel, M.D., Nicolas Boissel, M.D., Ph.D., Francoise Mechinaud, M.D., Adriana Balduzzi, M.D., Joerg Krueger, M.D., Carl H. June, M.D., Bruce L. Levine, Ph.D., Patricia Wood, M.D., Ph.D., Tetiana Taran, M.D., Mimi Leung, M.P.H., Karen T. Mueller, Pharm.D., Yiyun Zhang, Ph.D., Kapildeb Sen, Ph.D., David Lebwohl, M.D., Michael A. Pulsipher, M.D., and Stephan A. Grupp, M.D., Ph.D.

The authors' affiliations are as follows: the Departments of Pediatrics (S.L.M., S.A.G.) and Pathology and Laboratory Medicine (C.H.J., B.L.L.), Perelman School of Medicine, and Abramson Cancer Center (C.H.J., B.L.L.), University of Pennsylvania, and the Division of Oncology, Center for Childhood Cancer Research and Cancer Immunotherapy Program, Children's Hospital of Philadelphia (S.L.M., S.A.G.) — all in Philadelphia; the Department of Pediatrics and Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, and the Pauline Allen Gill Center for Cancer and Blood Disorders, Children's Health, Dallas (T.W.L.); the Department of Pediatric Hematology and Oncology, Oslo University Hospital, Oslo (J.B.); the Department of Pediatric Hematology and Oncology, Hospital Sant Joan de Deu Barcelona, Barcelona (S.R.); the Department of Pediatrics and Internal Medicine, University of Utah, Salt Lake City (M.B.); the Department of Pediatrics, Faculty of Medicine, University of Montreal, and the Hematology Oncology Division and Charles-Bruneau Cancer Center, Centre Hospitalier Universitaire Sainte-Justine Research Center, Montreal (H.B.), and the Division of Haematology/Oncology/Bone Marrow Transplantation, Hospital for Sick Children, Toronto (J.K.) — all in Canada; the Division of Stem Cell Transplantation and Immunology, Hospital for Children and Adolescents, University Hospital Frankfurt, Frankfurt, Germany (P.B.); the Division of Pediatric Blood and Marrow Transplant, University of Minnesota, Minneapolis (M.R.V.,

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REFERENCES

1. Maude SL, Teachey DT, Rheingold SR, et al. Sustained remissions with CD19-specific chimeric antigen receptor (CAR)-modified T cells in children with relapsed/refractory ALL. J Clin Oncol 2016;34:Suppl 15:3011. abstract.

2. Grupp SA, Maude SL, Shaw PA, et al. Durable remissions in children with relapsed/refractory ALL treated with T cells engineered with a CD19-targeted chimeric antigen receptor (CTL019). Blood 2015; 126:681. abstract.

3. Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Mol Ther 2009;17:1453-64.

4. Grupp SA, Laetsch TW, Buechner J, et al. Analysis of a global registration trial of the efficacy and safety of CTL019 in pediatric and young adults with relapsed/refractory acute lymphoblastic leukemia (ALL). Blood 2016;128:221. abstract.

5. Janetzki S, Britten CM, Kalos M, et al. "MIATA"-minimal information about T cell assays. Immunity 2009;31:527-8.

6. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. N Engl J Med 2013;368:1509-18.

7. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 2006; 24:1917-23.

8. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016;34:4381-9.

9. Shah B, Huynh V, Sender LS, et al. High rates of minimal residual disease-negative (MRD-) complete responses (CR) in adult and pediatric and patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) treated with KTE-C19 (anti-CD19 chimeric antigen receptor [CAR] T cells): preliminary results of the ZUMA-3 and ZUMA-4 trials. Blood 2016; 128:2803. abstract.

10. Lee DW, Stetler-Stevenson M, Yuan CM, et al. Long-term outcomes following CD19 CAR T cell therapy for B-ALL are superior in patients receiving a fludarabine/cyclophosphamide preparative regimen and post-CAR hematopoietic stem cell transplantation. Blood 2016;128:218. abstract.

11. Gardner R, Finney O, Smothers H, et al. CD19CAR T cell products of defined CD4:CD8 composition and transgene expression show prolonged persistence and durable MRD-negative remission in pediatric and young adult B-cell ALL. Blood 2016;128:219. abstract.

12. Sabatino M, Choi K, Chiruvolu V, Better M. Production of anti-CD19 CAR T cells for ZUMA-3 and -4: phase 1/2 multicenter studies evaluating KTE-C19 in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (R/R ALL). Blood 2016;128:1227. abstract.

13. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385:517-28.

14. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med 2013;5:177ra38.

15. Long AH, Haso WM, Shern JF, et al. 4-1BB costimulation ameliorates T cell exhaustion induced by tonic signaling of chimeric antigen receptors. Nat Med 2015;21: 581-90.

16. Lee DW, Stetler-Stevenson M, Yuan CM, et al. Safety and response of incorporating CD19 chimeric antigen receptor T cell therapy in typical salvage regimens for children and young adults with acute lymphoblastic leukemia. Blood 2015;126: 684. abstract.

17. Abramson JS, Palomba ML, Gordon LI, et al. CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T-cell product JCAR017 (TRANSCEND NHL 001). J Clin Oncol 2017;35:Suppl 15:7513. abstract.

18. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129:3322-31.

19. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126:2123-38.

20. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med 2015;7: 303ra139.

21. Gardner R, Leger KJ, Annesley CE, et al. Decreased rates of severe CRS seen with early intervention strategies for CD19 CAR-T cell toxicity management. Blood 2016;128:586. abstract.