ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

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ABSTRACT

BACKGROUND

Patients with diffuse large B-cell lymphoma or follicular lymphoma that is refractory to or that relapses after immunochemotherapy and transplantation have a poor prognosis. High response rates have been reported with the use of T cells modified by chimeric antigen receptor (CAR) that target CD19 in B-cell cancers, although data regarding B-cell lymphomas are limited.

METHODS

We used autologous T cells that express a CD19-directed CAR (CTL019) to treat patients with diffuse large B-cell lymphoma or follicular lymphoma that had relapsed or was refractory to previous treatments. Patients were monitored for response to treatment, toxic effects, the expansion and persistence of CTL019 cells in vivo, and immune recovery.

RESULTS

A total of 28 adult patients with lymphoma received CTL019 cells, and 18 of 28 had a response (64%; 95% confidence interval [CI], 44 to 81). Complete remission occurred in 6 of 14 patients with diffuse large B-cell lymphoma (43%; 95% CI, 18 to 71) and 10 of 14 patients with follicular lymphoma (71%; 95% CI, 42 to 92). CTL019 cells proliferated in vivo and were detectable in the blood and bone marrow of patients who had a response and patients who did not have a response. Sustained remissions were achieved, and at a median follow-up of 28.6 months, 86% of patients with diffuse large B-cell lymphoma who had a response (95% CI, 33 to 98) and 89% of patients with follicular lymphoma who had a response (95% CI, 43 to 98) had maintained the response. Severe cytokine-release syndrome occurred in 5 patients (18%). Serious encephalopathy occurred in 3 patients (11%); 2 cases were self-limiting and 1 case was fatal. All patients in complete remission by 6 months remained in remission at 7.7 to 37.9 months (median, 29.3 months) after induction, with a sustained reappearance of B cells in 8 of 16 patients and with improvement in levels of IgG in 4 of 10 patients and of IgM in 6 of 10 patients at 6 months or later and in levels of IgA in 3 of 10 patients at 18 months or later.

CONCLUSIONS

CTL019 cells can be effective in the treatment of relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. High rates of durable remission were observed, with recovery of B cells and immunoglobulins in some patients. Transient encephalopathy developed in approximately one in three patients and severe cytokine-release syndrome developed in one in five patients. (Funded by Novartis and others; ClinicalTrials.gov number, NCT02030834.)

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Diffuse large B-cell lymphoma, the most common non-Hodgkin's lymphoma, is successfully treated in about two thirds of patients with rituximab-based immunochemotherapy.[1,2] When current frontline immunochemotherapy fails, high-dose chemotherapy with autologous stem-cell transplantation can lead to long-term disease-free survival. However, only half of these patients with relapsed or refractory disease are candidates for this approach, and for most patients treated since the introduction of rituximab, the expected rate of 3-year event-free survival after autologous stem-cell transplantation is only approximately 20%.[3]

Patients with follicular lymphoma, the second most frequently occurring non-Hodgkin's lymphoma, have an excellent prognosis after receiving frontline rituximab-based therapies; however, in 20% of patients with follicular lymphoma, relapse occurs within 2 years after initial immunochemotherapy. These patients with early relapse have a poor prognosis, with a rate of 5-year overall survival of only 50% when they are treated with currently available therapies.[4,5] Among patients with relapsed follicular lymphoma that is refractory to rituximab and to alkylating-agent–based therapy, treatment with idelalisib or copanlisib, the only agents that have been approved by the Food and Drug Administration (FDA) for such patients, is associated with a median response duration of 10.8 and 12.2 months, respectively.[6,7] Thus, new therapeutic approaches are needed for patients with follicular lymphoma who have early progression of disease after immunochemotherapy and for those with disease that is refractory to rituximab and alkylating agents.

Adoptive immunotherapy that incorporates T cells that have been genetically engineered to express a chimeric antigen receptor (CAR) for the pan–B-cell CD19 antigen has been associated with high response rates in patients with relapsed or refractory B-cell cancers, including acute lymphoblastic leukemia, chronic lymphocytic leukemia, and B-cell non-Hodgkin's lymphoma.[8-15] CARs generally couple an antibody-derived, single-chain Fv domain to an intracellular T-cell–receptor zeta chain and a costimulatory receptor-signaling domain. After lentiviral-vector gene transfer, CTL019-engineered T cells express an anti-CD19 CAR, with the T-cell activation signal provided by the CD3-zeta domain and the costimulatory signal provided by the CD137 (4-1BB) domain.[16]

Long-lasting, complete remission has been reported after CTL019 therapy in children with lymphoblastic leukemia and in adult patients with chronic lymphocytic leukemia, and these remissions have been associated with a high level of in vivo expansion and persistence of CTL019 cells and with B-cell aplasia.[8,10] We report the results of our clinical study, which shows the efficacy of CTL019 therapy in cohorts of patients with relapsed or refractory diffuse large B-cell lymphoma or follicular lymphoma, and provide up to 3 years of follow-up data. CTL019 cells rapidly induced complete responses in a high proportion of these patients. Furthermore, these remissions were durable and were accompanied by B-cell and immunoglobulin recovery in some patients.

METHODS

STUDY DESIGN

This case-series study was designed by the principal investigator and conducted at the Hospital of the University of Pennsylvania. Patients were eligible if they had CD19+ diffuse large B-cell lymphoma or follicular lymphoma with no curative treatment options, a limited prognosis (<2 years of anticipated survival), and a partial response to or stable disease after the most recent therapy. Patients with diffuse large B-cell lymphoma were eligible if they had measurable disease after primary and salvage therapies, had relapsed or residual disease after autologous stem-cell transplantation, or were not eligible for autologous or allogeneic stem-cell transplantation. Patients with follicular lymphoma were eligible if they had measurable progression of disease less than 2 years after the second line of immunochemotherapy (excluding single-agent monoclonal antibody therapy). Enrolled patients received CTL019 infusions between March 11, 2014, and August 2, 2016; clinical outcome data were up to date as of May 7, 2017.

Leukapheresis products were stimulated with paramagnetic beads coated with antibodies to CD3 and CD28 and were transduced with the CD19-BB-zeta transgene, as described previously.[16,17] After leukapheresis, patients could receive bridging therapy at the discretion of their treating physician during the manufacture of CTL019 cells. Once successful production and release testing of CTL019 cells were confirmed, patients underwent staging followed by chemotherapy to

deplete T lymphocytes. Lymphodepleting regimens were chosen by the investigator on the basis of each patient's treatment history, blood counts, and organ function (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). CTL019 cells were infused 1 to 4 days after the completion of lymphodepleting chemotherapy. The dose, as specified in the protocol (available at NEJM.org), was 1.00×10^8 to 5.00×10^8 CTL019 cells.

The primary objective of the study was the overall response rate at 3 months for all patients receiving the protocol-specified dose of CTL019 cells, with the response evaluated with the use of the 1999 International Working Group response criteria; complete response was confirmed on ^{18}F-fluorodeoxyglucose–positron-emission tomography.[18,19] The response rate was summarized, and 95% exact confidence intervals were calculated. Sample size was approximated on the basis of a response rate of 50% (15 of 30 patient responses), with 95% confidence in a true response rate of more than 30%. Response rates for diffuse large B-cell lymphoma and follicular lymphoma were analyzed separately as secondary objectives. Progression-free survival and duration of response were estimated with the use of the Kaplan–Meier method. The median survival time and probability of survival were estimated with the use of 95% confidence intervals. The number of patients enrolled versus the number who received an infusion was described to assess feasibility and manufacturing success.

Blood and marrow samples were collected at prespecified times. Correlative studies examined biomarkers of outcome with the use of immunohistochemical analysis for biopsy specimens of tumors, with flow cytometry for the analysis of lymphocytic phenotypes of blood and marrow, and with polymerase-chain-reaction (PCR) assays for the detection of CTL019 DNA.[9] Additional details regarding study design are provided in Figure S1 in the Supplementary Appendix.

STUDY OVERSIGHT

The study was approved by the institutional review board at the Hospital of the University of Pennsylvania. The data were collected and analyzed and the manuscript was prepared independently at the University of Pennsylvania. The study sponsor provided financial support but played no role in the analysis of the data or the writing of the manuscript. All the authors discussed and interpreted the study results and analyses and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. No one who is not an author contributed to the writing of the manuscript. All the patients provided written informed consent.

RESULTS

PATIENT CHARACTERISTICS

A total of 38 patients were enrolled in the study, and 28 patients received treatment as specified in the protocol. Ten patients did not receive treatment as specified in the protocol owing to rapid disease progression with clinical deterioration (4 patients, 3 with diffuse large B-cell lymphoma and 1 with follicular lymphoma), an insufficient T-cell count for the manufacture of CTL019 cells (5 patients, all with diffuse large B-cell lymphoma), and withdrawal of consent (1 patient, with diffuse large B-cell lymphoma). T-cell manufacturing was unsuccessful for 5 patients, all of whom had absolute lymphocyte counts of 300 per cubic millimeter or fewer (3 had poor T-cell growth, and 2 did not undergo apheresis owing to the degree of lymphopenia). The characteristics of patients who received CTL019 infusion are shown in Table 1, and in Table S2 in the Supplementary Appendix. Twelve patients (86%) with diffuse large B-cell lymphoma met stringent criteria for refractory disease, which was defined as disease for which the best response to chemotherapy was progressive or stable disease (with stable disease defined as being <12 months in duration after at least four cycles of first-line therapy or two cycles of second-line or later therapy) or relapse within 12 months or less after autologous stem-cell transplantation. Eight patients (57%) with follicular lymphoma met the criteria for double-refractory follicular lymphoma, which was defined as progressive disease within 6 months after the last dose of rituximab and the last dose of an alkylating agent (Table 1).

OUTCOMES

The median total CTL019-cell dose was 5.00×10^8 (range, 1.79×10^8 to 5.00×10^8), and the median CTL019-cell dose per kilogram of body weight was 5.79×10^6 (range, 3.08×10^6 to 8.87×10^6). The median number of days from apheresis to infusion was 39 (range, 27 to 145); 10 of 28 patients

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Patients Enrolled (N=38)		Patients Treated (N=28)	
	Follicular Lymphoma (N=15)	Diffuse Large B-Cell Lymphoma (N=23)	Follicular Lymphoma (N=14)	Diffuse Large B-Cell Lymphoma (N=14)
Age — yr				
Median	62	56	59	58
Range	43–72	25–77	43–72	25–77
Female sex — no. (%)	8 (53)	7 (30)	7 (50)	3 (21)
Previous therapies				
Median	5	3	5	3
Range	2–10	1–8	2–10	1–8
Advanced stage disease — no. (%)*	13 (87)	17 (74)	12 (86)	9 (64)
Bone marrow involved — no./total no. (%)	4/15 (27)	4/21 (19)	4/14 (28)	3/14 (21)
Elevated lactate dehydrogenase — no. (%)	10 (67)	16 (70)	9 (64)	8 (57)
ECOG performance-status score†				
Median	0	1	0	1
Range	0–1	0–1	0–1	0–1
Refractory diffuse large B-cell lymphoma — no. (%)‡	—	21 (91)	—	12 (86)
Double refractory follicular lymphoma — no. (%)§	9 (60)	—	8 (57)	—
Previous stem-cell transplantation — no. (%)				
Autologous	3 (20)	9 (39)	3 (21)	7 (50)
Allogeneic	1 (7)	0	1 (7)	0

* Advanced stage disease is defined as stage III or IV according to the modified Ann Arbor staging system.[20]

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher numbers indicating increasing disability. A score of less than 3 indicates that the patient is at least ambulatory and capable of all self-care, although he or she may be unable to carry out any work activities, and that the patient is out of bed more than 50% of waking hours.

‡ Refractory diffuse large B-cell lymphoma is defined as disease in which progressive or stable disease is considered to be the best response to chemotherapy (with stable disease defined as disease that is less than 12 months in duration after the patient has undergone at least four cycles of first-line therapy or two cycles of second-line, third-line, or later therapy) or as relapse <12 months after autologous stem-cell transplantation. Patients must have received an anti-CD20 monoclonal antibody (unless they had negative test results for CD20) and an anthracycline as one of their previous treatment regimens.

§ Double-refractory follicular lymphoma is defined as progression of disease within 6 months after receiving the last dose of rituximab and within 6 months after receiving the last dose of an alkylating agent.

received bridging therapy, which was administered after apheresis and before lymphodepleting chemotherapy. At 3 months, 18 of 28 patients had a response (64%; 95% confidence interval [CI], 44 to 81). Among patients with diffuse large B-cell lymphoma, 7 of 14 had a response (50%; 95% CI, 23 to 77), and among patients with follicular lymphoma, 11 of 14 had a response (79%; 95% CI, 49 to 95). Three patients with follicular lymphoma who had a partial response at 3 months had a complete response by 6 months; 1 patient continued to have a partial response at 6 months and had progressive disease at 1 year. One patient with diffuse large B-cell lymphoma who had a partial response at 3 months had a complete response by 6 months; another such patient, who had a partial response at 3 months and 6 months, ultimately had progressive disease.

Among all patients, 16 of 28 had a complete response at 6 months (57%; 95% CI, 37 to 76), including 6 of 14 patients with diffuse large B-cell lymphoma (43%; 95% CI, 18 to 71) and 10 of 14 patients with follicular lymphoma (71%; 95% CI, 42 to 92). All patients in complete remission by 6 months remained in remission at 7.7 to 37.9 months (median, 29.3 months) after induction. For all patients who received a CTL019 infusion, the median progression-free survival had not been

reached at the cutoff date for data collection (May 7, 2017). At a median follow-up of 28.6 months, 57% of all patients remained progression-free (95% CI, 36 to 73). Among patients with diffuse large B-cell lymphoma, median progression-free survival was 3.2 months (95% CI, 0.9 to not reached), and 43% of these patients were progression-free at median follow-up (95% CI, 18 to 66). Among patients with follicular lymphoma, median progression-free survival was not reached, and 70% (95% CI, 38 to 88) were progression-free at the median follow-up of 28.6 months. The median response duration was not reached: at median follow-up, 86% of patients with diffuse large B-cell lymphoma who had a response (95% CI, 33 to 98) and 89% of patients with follicular lymphoma who had a response (95% CI, 43 to 98) had maintained the response (Fig. 1).

EFFICACY IN SUBTYPES OF DIFFUSE LARGE B-CELL LYMPHOMA

In order to determine the cell of origin, immunohistochemical studies were performed for 12 patients with diffuse large B-cell lymphoma who received CTL019 cells.[21] Among these patients, 7 had a germinal-center phenotype and 5 had a non–germinal-center phenotype; 4 of the former group (57%) and 2 of the latter group (40%) had a complete response. Fluorescence in situ hybridization (Vysis) performed with *MYC* (8q24), *BCL2* (18q21), and *BCL6* (3q27) break-apart probes was used to detect "double-hit lymphoma" (*MYC* translocation with *BCL2* translocation, *BCL6* translocation, or both) in 5 patients with germinal-center tumors.[22] Two patients had double-hit lymphoma; both had complete responses. Three of 7 patients with germinal-center tumors had large-cell transformation of follicular lymphoma, one of which was a double-hit lymphoma. All 3 patients with large-cell transformation of follicular lymphoma had complete responses. Thus, a single treatment with CTL019 cells can be efficacious in relapsed and refractory germinal-center and non–germinal-center diffuse large B-cell lymphoma, double-hit lymphoma, and transformed follicular lymphoma. As of May 2017, no patient who had a complete response had a relapse.

IN VIVO EXPANSION AND PERSISTENCE OF CTL019 CELLS

After infusion, median peak expansion of CTL019 cells in the blood occurred at 8 days (range, 6 to 14) in patients who had a response and at 10 days (range, 6 to 14) in patients who had not had a response (Fig. S3 in the Supplementary Appendix). No significant difference was noted between peak CD8–CTL019 expansion and peak CD4–CTL019 expansion between patients who did and those who did not have response. Among 16 patients who had a complete response, 14 had consistently detectable levels of CTL019 DNA between 6 and 24 months after infusion of CTL019 cells. Two patients with diffuse large B-cell lymphoma lost detectability of CTL019 DNA — 1 at 3 months and 1 at 4 months — but continued to have a complete response at 23 and 29 months, respectively.

B-CELL DEPLETION AND RECOVERY OF HUMORAL IMMUNITY

We measured levels of CD19+ B cells in blood to assess CTL019 activity. Transient B-cell depletion occurred after CTL019 cells were infused in all 16 patients who had a complete response. Polyclonal B-cell recovery was sustained in 8 of 16 patients (50%) during continuous complete response. The median time to onset of sustained B-cell recovery was 6.7 months (range, 0.3 to 12) for these 8 patients. Transient B-cell depletion was also observed after CTL019 infusion in 10 of 12 patients who had a partial response (2 patients) or progressive disease (8 patients). Two patients without B-cell depletion had early progressive disease despite detectable in vivo expansion of CTL019 cells in blood, as detected with flow cytometry and quantitative PCR (qPCR) assay (data not shown).

Twelve patients who had a complete response 6 months after infusion of CTL019 cells and who were not receiving prophylactic intravenous immune globulin (IVIG) were monitored for worsening hypogammaglobulinemia, frequency of infections, and immunoglobulin recovery. Two of these patients began treatment with IVIG for hypogammaglobulinemia with recurrent sinopulmonary infections at 12 and 22 months after CTL019 infusion; IgG levels in these patients had decreased by 66% and 13%, respectively, from baseline levels. Ten patients (5 with diffuse large B-cell lymphoma and 5 with follicular lymphoma) did not receive IVIG at any time after receiving CTL019 cells. These 10 patients were followed for changes in immunoglobulin levels and B-cell recovery. The median follow-up for these 10 pa-

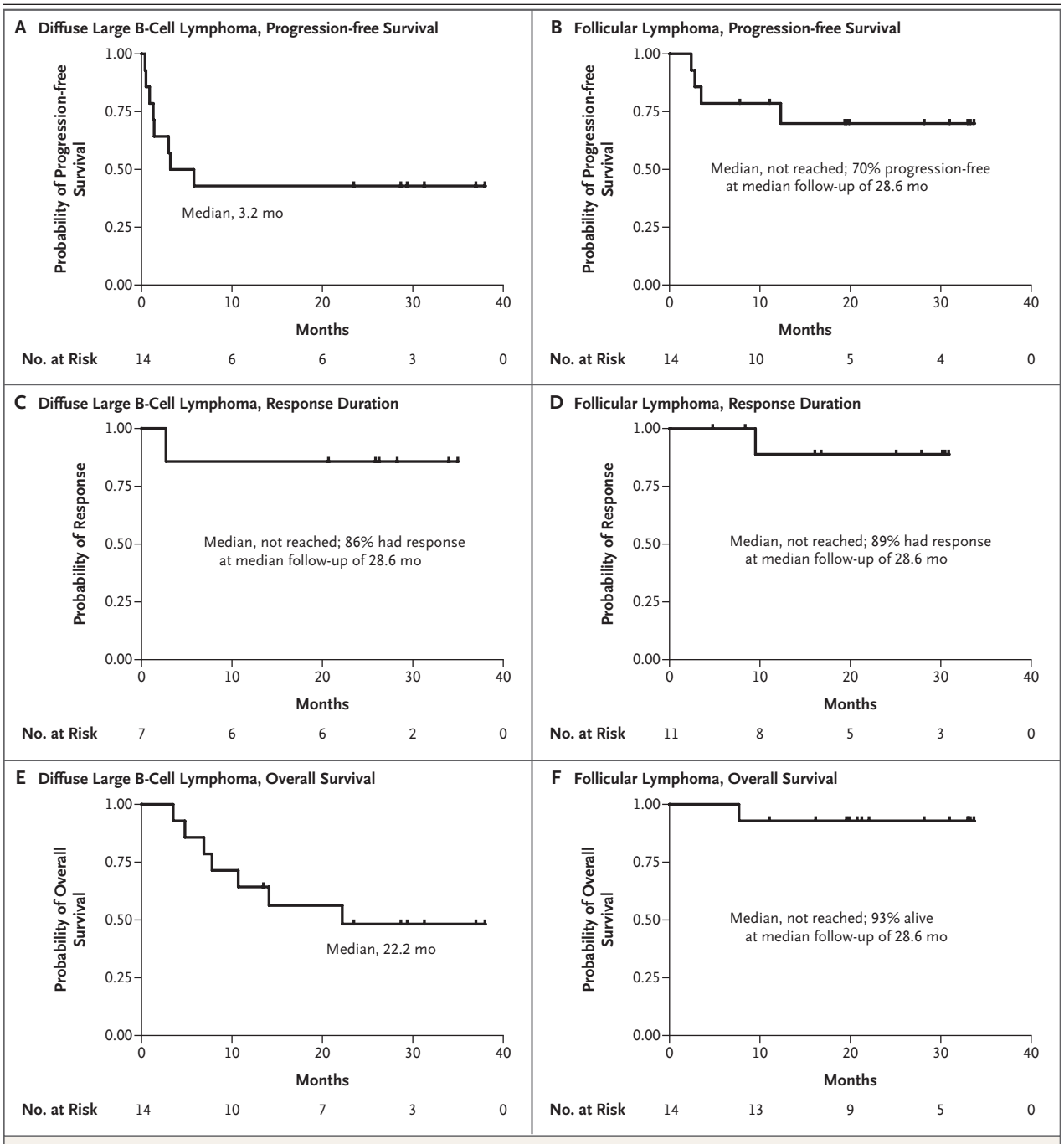

Figure 1. Progression-free Survival, Response Duration, and Overall Survival.

tients is 22.5 months (range, 11 to 34) (Figs. S4 and S5 in the Supplementary Appendix). At 18 months after CTL019 infusion, 3 of 10 patients (30%) had definite increases in IgG levels, including 2 patients who had previously had lower-than-normal baseline IgG levels and who had normal values after treatment (Fig. S4A in the Supplementary Appendix). Two patients whose nadir IgG level returned to normal also had recovery of normal IgA levels (47% and 22% above baseline levels, respectively, at 30 and 24 months after CTL019 infusion). One patient whose IgG

Table 2. Adverse Events of Special Interest That May Have Been Related to CTL019 Therapy.*

Adverse Event	Grade					Total Events	Grade 3 or Higher
	1	2	3	4	5		
						number (percent)	
Cytokine release syndrome	0	11	4	1	0	16 (57)	5 (18)
Neurotoxicity	4	4	1	1	1	11 (39)	3 (11)
Encephalopathy	0	0	1	1	1	3 (27)	
Delirium	0	2	0	0	0	2 (18)	
Tremor	2	0	0	0	0	2 (18)	
Cognitive disturbance	1	0	0	0	0	1 (5)	
Confusion	0	1	0	0	0	1 (5)	
Involuntary movements	1	0	0	0	0	1 (5)	
Memory impairment	0	1	0	0	0	1 (5)	

* A list of all adverse events is provided in the Supplementary Appendix.

level recovered from its lowest point to baseline level 18 months after CTL019 infusion also had recovery of the IgA level to baseline at 24 months, indicating increasing production of IgG and IgA over time (Fig. S4B in the Supplementary Appendix). Levels of IgM normalized in 4 of 10 patients between 12 and 24 months after CTL019 infusion (Fig. S4C in the Supplementary Appendix). In 9 of 10 patients who did not receive IVIG, CTL019 DNA remained detectable on qPCR at follow-up 6 to 24 months after infusion. Thus, in patients with adult lymphoma who have a complete response after CTL019 infusion, immunoglobulin levels may improve despite molecular evidence of CTL019 persistence. Most patients do not need routine immunoglobulin replacement after CTL019 infusion.

TOXIC EFFECTS

All adverse events are described in Table S3 in the Supplementary Appendix. Adverse events of special interest that may at least possibly be related to CTL019 therapy are shown in Table 2. Cytokine-release syndrome was graded with the use of the Penn scale, a 4-point scale in which higher numbers reflect greater toxicity.[23]

Cytokine-release syndrome has been reported as a major source of toxic effects for patients receiving CD19–CAR–T-cell therapies.[8-10,12,24] Severe cytokine-release syndrome, which is defined as grade 3 or higher, is rapidly reversed with the administration of tocilizumab, an interleukin-6–receptor blocking antibody.[8,9] (See the protocol for additional information.) Five patients had severe cytokine-release syndrome. One patient was treated with tocilizumab, had a rapid reversal of symptoms, and had a complete response to treatment. No patients received glucocorticoids, and no deaths from cytokine-release syndrome occurred.

Eleven patients had neurologic toxic effects related to CTL019 therapy. Effects ranged from mild cognitive disturbance to global encephalopathy (grade 3 or higher); three patients had encephalopathy of grade 3 or higher (Table 2, and Table S3 in the Supplementary Appendix). With the exception of those in one patient, the neurologic symptoms were self-limiting and resolved fully within 1 week. In all patients who underwent brain imaging and whose spinal fluid was evaluated for neurotoxicity, neither cerebral edema nor infection was detected. One patient with follicular lymphoma who had encephalopathy had progressive neurologic deterioration that resulted in death. This patient had a history of optic atrophy and was the only patient who underwent fludarabine-based lymphodepletion. Postmortem examination of the brain revealed diffuse gliosis with severe, widespread neuronal loss and degeneration of white matter associated with an inflammatory process that involved dense macrophage infiltration of white matter, numerous microglial cells, and a moderate CD8+

T-cell infiltrate; there was no evidence of herpes simplex virus 1 or 2, cytomegalovirus, varicella–zoster virus, JC virus, adenovirus, or Epstein–Barr virus.

EXPLORATORY STUDIES FOR BIOMARKERS OF RESISTANCE TO CTL019 THERAPY

There was no significant difference in tumor burden between patients who had a response to CTL019 treatment (median tumor size, 22 cm^2; range, 3 to 100) and those who did not (median tumor size, 30 cm^2; range, 13 to 157). We examined pretreatment tumor biopsy specimens from 10 patients with diffuse large B-cell lymphoma, including 5 who had a response to treatment and 5 who did not have a response. A comparison of the results of immunohistochemical staining and quantitative immunohistochemical image analysis for the expression of PD-L1, PD1, LAG3, and TIM3 suggested that patients who had a response to CTL019 therapy tended to express lower levels of immune-checkpoint ligands (tumor cells) and receptors (immune cells), whereas those who did not have a response tended to have higher levels of expression of immune-checkpoint proteins. However, the limited number of patients studied did not provide the statistical power needed for stringent correlative analysis (Fig. S6 in the Supplementary Appendix).

Five patients who had progressive disease after CTL019 infusion underwent biopsy. One of these patients had loss of CD19 in tumor cells, and four had continued tumor-cell expression of CD19.

We did not discern any significant differences in the composition of CAR T-cell products between patients who did and those who did not have a response. CTL019 products from 10 patients with diffuse large B-cell lymphoma (5 who had a complete response and 5 who had progressive disease) were characterized phenotypically for T-cell subgroups (naive memory, central memory, effector memory, and terminal effector) and for activation and regulatory markers (CD62L, CD25, CD69, HLA-DR, CTLA4, FoxP3, and PD1). There were no significant differences in levels of these markers between patients who did have a response and those who did not. The majority of transduced and nontransduced T cells in the final product were effector memory cells (data not shown).

DISCUSSION

We report outcomes among patients receiving CD19-directed CAR T cells for the treatment of B-cell lymphomas who were followed for a median of 28.6 months (range, 3.5 to 37.9). In our study, 57% of adults who received CTL019 cells for relapsed or refractory diffuse large B-cell lymphoma or follicular lymphoma had a complete response. As of May 2017, no patient who had a complete response had a relapse or required additional therapy. It is noteworthy that our patients received personalized lymphodepleting regimens that were based on their response history, blood counts, and organ function and that the rate of complete response in our study is similar to the rates reported in studies that used cyclophosphamide–fludarabine, a less disease-specific and potentially more toxic lymphodepleting regimen.[12,15]

Persistence of CTL019 DNA, as determined by qPCR, was observed in 14 of 16 patients who had a complete response, with a median duration of persistence of 24 months (range, 6 to 24). Transient depletion of peripheral-blood CD19+ B cells occurred both in patients who did and in those who did not have a response to treatment. Among the 16 patients who did have a complete response, 8 had sustained polyclonal B-cell recovery that was not associated with relapse, despite recovery of normal CD19 B cells. It is possible that after malignant (and normal) CD19+ cells have been eliminated, the remaining CAR T cells are exhausted or inhibited by one of the immune checkpoint receptors, thereby allowing normal CD19+ B-cell recovery.

Potentially serious toxic effects that are specific to CAR T-cell therapy are the cytokine-release syndrome and neurotoxicity. In our patients, the cytokine-release syndrome was less frequent and less severe than previously reported for the use of CTL019 cells in the treatment of lymphoblastic leukemia and chronic lymphocytic leukemia. The cytokine-release syndrome was self-limiting and was not associated with response to therapy. Neurotoxicity was self-limiting in all but one patient.

Patients who have diffuse large B-cell lymphoma that is progressive or unresponsive to primary and salvage treatments and those who have relapse within 12 months after autologous stem-cell transplantation have an estimated rate of response to currently available therapies of 20 to 30%

and a median overall survival of approximately 6 months.[25] Similarly, patients with follicular lymphoma that is refractory to treatment with rituximab and alkylating agents who have progressive disease when treated with idelalisib have a survival rate of only 22% at 2 years.[6] Our study included such patients with a poor prognosis and no available curative treatment options. Thus, our observed complete response rates of 43% for patients with diffuse large B-cell lymphoma and 71% for those with follicular lymphoma, with sustained remissions lasting up to 3 years after a single dose of CTL019 cells, support further development of this approach. The results of two large, multicenter trials of CD19–CAR–T-cell therapy in patients with relapsing or refractory aggressive B-cell lymphomas have recently been reported.[26,27] Complete response rates at 3 months and 6 months were similar to those reported for the cohort with diffuse large B-cell lymphoma in our study. At present, the reported median follow-up for these larger studies is less than 9 months. If these clinical trials confirm the durability of remissions shown in our case series, CD19–CAR–T-cell therapy may become a useful treatment approach for relapsed or refractory B-cell lymphomas.

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