Transplantation and Cellular Therapy 000 (2022) 1–7

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Immunotherapy

Point-of-care anti-CD19 CAR T-cells for treatment of relapsed and refractory aggressive B-cell lymphoma

Meirav Kedmi[1,2,3,a,*], Roni Shouval[1,2,4,5,a], Shalev Fried[2], David Bomze[2], Joshua Fein[6], Zachary Cohen[2], Ivetta Danilesko[1,2], Noga Shem-Tov[1,2], Ronit Yerushalmi[1,2], Elad Jacoby[2,7], Michal Besser[8,9], Avichai Shimoni[1,2], Arnon Nagler[1,2,b], Abraham Avigdor[1,2,b]

[1] *Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[2] *Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*
[3] *The Mina & Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Israel*
[4] *Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[5] *Weill Cornell Medical College, New York, New York*
[6] *University of Connecticut Medical Center, Farmington, Connecticut*
[7] *Division of Pediatric Hematology, Oncology and BMT, Chaim Sheba Medical Center, The Edmond and Lily Safra Children's Hospital, Tel-Hashomer, Israel*
[8] *Department of Clinical Microbiology and Immunology, Sackler School of Medicine, Tel-Aviv, Israel*
[9] *Ella Lemelbaum Institute for Immuno Oncology, Chaim Sheba Medical Center, Tel-Hashomer, Israel*

Article history:
Received 7 November 2021
Accepted 17 February 2022

Key Words:
Aggressive B-cell lymphoma
CAR T-cell
Allogeneic stem cell transplantation
Point of care

A B S T R A C T

Anti CD19 chimeric antigen receptor (CAR) T-cell therapy has transformed the care of relapsed and refractory aggressive B-cell lymphoma. However, financial toxicity and manufacturing time represent barriers to its widespread implementation. Study applicability, toxicity, and efficacy of a locally produced autologous CD19-directed CAR T-cell product were studied. We performed a phase 1b/2 clinical trial with a point-of-care (POC) CAR T-cell product that contains a CD28 costimulatory domain. Adult patients with aggressive B-cell lymphoma or transformed low-grade lymphoma who received at least 2 prior regimens were eligible. A total of 73 patients, with a median age of 49 years, met inclusion criteria. CAR T-cell production time from apheresis was 10 days (interquartile range 10-11), negating the need for bridging chemotherapy. Overall and complete response rates were 62.5% and 37.5%. Median progression-free and overall survival were 3.7 and 12.1 months, respectively. Overall and progression-free survival at 12 months were 52.1% (confidence interval [CI]: 40.8%-66.5%) and 40% (CI: 30%-53.7%), respectively. Patients who achieved response had longer progression-free and overall survival. Grade 3-4 cytokine release syndrome was observed in 9.5% of the patients, and immune effector cell-associated neurotoxicity syndrome grade 3-4 in 21.9%. No deaths occurred due to CAR T-cell toxicity. Fifteen patients (20%) underwent allogeneic stem cell transplantation at a median time of 60 days after CAR T-cell therapy; 8 were alive at last follow-up. Of the 6 patients who underwent the transplantation in complete response 2 deceased because of toxicity. POC CAR T-cells are a feasible therapeutic option in aggressive B-cell lymphoma. They provide good efficacy while minimizing production time and the need for bridging therapy.

Relapse of aggressive B-cell lymphoma (ABCL) poses a significant clinical challenge. Current standard second-line therapy in intent to cure is based on platinum-containing regimens and autologous stem cell transplantation (ASCT) [1]. This will achieve roughly 20% to 30% long-term survival [2]. Many of the patients are elderly and therefore are not ASCT candidates. As a result, until recently, these patients were considered incurable.

Transduced T cells expressing chimeric antigen receptor targeting CD19 (CD19 CAR T-cells) became the standard of care for multiply relapsed ABCL. They constitute a form of adoptive immunotherapy that was found to be effective in B acute lymphoblastic leukemia, B-cell non-Hodgkin lymphoma, and to a somewhat lesser degree in chronic lymphocytic leukemia [3]. The long-term survival post CAR T-cell therapy in ABCL is reported to be 40% [4,5]. Lymphodepletion, mostly

Financial disclosure: See Acknowledgments on page XXXX.

*Correspondence and reprint requests: Meirav Kedmi, Hematology Hospitalization Center, Division of Hematology & Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel

E-mail address: Meirav.kedmi@sheba.health.gov.il (M. Kedmi).

[a] M.K. and R.S. contributed equally to the manuscript.

[b] A.N. and A.A. are joint senior authors and contributed equally to the manuscript.

https://doi.org/10.1016/j.jtct.2022.02.017

with cyclophosphamide and fludarabine before CAR T-cell infusion, is necessary to enhance cellular efficacy before CAR T-cell infusion [6]. CAR T-cell therapy most common side effects are cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and hematological toxicity. However, additional long-term side effects have been described [7]. Real-world experience with CAR T-cell therapy for ABCL with the products approved by the Food and Drug Administration demonstrates a similar efficacy and toxicity profile as reported in the clinical trials [8,9].

The COVID-19 pandemic brought significant difficulties with CAR T-cell therapy, from patient selection to timing, manufacturing, and delivery issues [10,11]. Point-of-care, academic, CAR T-cell products have been shown before to be efficacious [12]. The possibility to provide local CAR T-cell product became an advantage during the pandemic.

Since November 2017, we started treating adult patients with relapsed or refractory ABCL with our locally produced anti CD19 CAR T-cell product that contains CD28 costimulatory domain (NCT02772198). Peripheral blood mononuclear cells (PBMC) are isolated, activated, and transduced with a gamma retrovirus encoding for a CD19 CAR [13–15]. The median turnover time is 10 days (interquartile range [IQR] 10-11).

The question of allogeneic stem cell transplantation (allo-SCT) as consolidation for CAR T-cell therapy remains unanswered [16]. It is clear, though, that most patients will relapse after CAR T-cell therapy, and there is an unmet need for this patient population. When we first started our CAR T-cell trial we consolidated responding patients with allo-SCT. Later we switched to performing transplantation only on patients in partial response or relapse after CAR T-cell therapy. Here we describe the results of our experience with our in-house CAR T-cell product in 73 ABCL patients. We also describe the outcomes of the patient population that underwent allo-SCT after CAR T-cell therapy.

METHODS

Study design

This is a phase 1b/2 trial (NCT02772198) that was approved by the Sheba Medical Center institutional review board and the Israeli Ministry of Health. All authors participated in the data analysis and have full access to the clinical data. Individual participant data will not be shared. Inclusion criteria were age above 18 years, failure of at least 2 prior therapeutic protocols, a CD3 count greater than 250/μL, no immunosuppressive treatment, as well as preserved heart, lung, kidney, and liver function. Patients with uncontrolled rapidly progressing disease or active central nervous system involvement were excluded, as well as patients with active hepatitis B or C, HIV, and pregnant women [13,14]. Until the end of 2018, we limited our study to patients aged 55 or younger, since then advanced age was no longer an exclusion criterion. Bridging chemotherapy was allowed.

CAR T-cell production and Administration

The retroviral supernatant was generated from the CD19 CAR producer line PG13-CD19-CAR-H3, which was provided by the National Cancer Institute (NCI). A plasmid encoding the CD19 CAR containing the mouse stem-cell virus gamma-retroviral backbone engineered to a single-chain fragment variable (scFv) derived from the mouse anti-CD19 hybridoma, FMC63, fused to intracellular domains from human CD28 and CD3-ζ, was used for viral vector production. Fresh leukapheresis product was used for CD19 CAR T-cell production. PBMCs were isolated from the apheresis product by density gradient with Ficoll-Hypaque. 400×10e6 PBMC were re-suspended at the concentration of 1×10^6 cells/mL. After 2 days, 60×10^6 cells were transduced with the CD19 CAR retroviral vector and the rest were discarded. The CD19 CAR T-cells quality that included cell identity, transduction efficacy, cell count, viability, potency, impurity and replication competent retrovirus polymerase chain reaction, was controlled throughout the manufacturing process. Sterility was tested on day 8 (+1). Quality control passed, if no growth was seen following membrane filtration. The test was validated for anaerobic, aerobic and fungal growth. A preliminary result was available on the day of infusion. Mycoplasma test was validated by nested polymerase chain reaction on day 9 (+1) and the result was available before infusion. On the day of infusion, cells were washed, counted and 1×10^6 CD19 CAR expressing cells/kg were resuspended in 100 mL 0.9% sodium chloride (Baxter, Ltd., Marsa, Malta) containing 2.5% human albumin and 300 IU/mL IL-2. The fresh cell product was delivered to the patient for immediate infusion [14]. Lymphodepletion included fludarabine 25 mg/m^2 × 3 days (days −4 to −2) and cyclophosphamide 900 mg/m^2 × 1 day (day −2), followed by infusion (day 0) of 1×10^6 CAR+ transduced cells /kg recipient [13,14]. This study was initiated at 1×10^6 CAR+ cell/kg based on initial results from previous studies with FMC63-28-zeta CARs (NCI: NCT00924326 and NCT03827343). No dose escalation was planned. Data on CAR T-cell persistence was not prospectively collected.

Response assessment and Definitions

The study's primary endpoints were response on day 28, best response, and safety. Response assessment was done with a PET-CT scan and interpreted according to the Lugano criteria [17]. Overall response rate (ORR) was defined as the proportion of subjects with either a complete response (CR) or partial response (PR). Day 28 response was defined as response assessment in the first 28 days (±7 days; whichever is closest to day 28) after CAR T-cell infusion. Best response was defined as best achieved response after CAR T-cell infusion. Response was calculated relative to the most recent disease assessment before infusion of CAR T-cells. Time to best response was defined as the time from the date of CAR T-cell infusion to the date documented the best response. CRS and ICANS were graded as per American Society for Transplantation and Cellular Therapy guidelines [18].

Secondary endpoints were overall survival (OS), progression-free survival (PFS), and production feasibility. OS was defined as the time from CAR T-cell infusion to death of any cause. PFS was defined as the time CAR T-cell infusion to the date of either first documented relapse, progression, or death from any cause. Patients were censored if they were event free or received anticancer treatment after CAR T.

Statistical analysis

Continuous variables were summarized by number, mean, standard deviation, minimum, median, maximum and sum. Categorical variables were summarized by frequencies, percentages, and two-sided 95% CIs. For time-to-event variables, the Kaplan-Meier method was used for descriptive summaries and log-rank test for comparison of survivals. Cox regression was used for multivariate survival analysis. Correlations between categorical and continuous variables and outcomes were done using logistic and linear regression, respectively. The data were analyzed using the R version 3.5.0. Day 0 was defined as the day of CAR T−cell administration.

RESULTS

Patients

From November 2017 until December 2020, we enrolled 73 adult ABCL patients who received CAR T-cells. Patients' characteristics are depicted in Table 1. Median age was 49 (range 20-73), 25 of the patients (34%) were older than 55 and 45 (61.6%) were male. The Karnofsky performance status was 90% to 100% in 74%, 70% to 80% in 15.1%, and lower in the others. Most patients (72.6%) had stage III/IV disease at apheresis. Twenty-five (34.2%) patients had previous ASCT, and 4 (5.5%) had allogeneic stem cell transplantation (alloSCT). Forty-six patients (63%) had 3 or more prior lines of therapy. Twelve (16.4%) had bulky disease at apheresis, and 6 (8.2%) had a history of central nervous system involvement. Sixty-three (86.3%) had stable or progressive disease at screening, and 37 (51.4%) were primary refractory.

Disease

The cohort included 28 (38%) patients with diffuse large B-cell lymphoma, 22 (30%) with transformed low-grade lymphoma, of them 8 patients with Richter's transformation (RT), 12 (16%) with primary mediastinal B-cell lymphoma, 7 (9%) with high-grade B-cell lymphoma (5 of them with double-hit lymphoma) and 4 patients (5%) with mantle cell lymphoma (Table 1). Cell of origin, which was determined by the Hans criteria, was germinal center in 25 (34.2%) and nongerminal center in 24 (32.9%) [19]; status was unknown in 24 cases.

CAR T-cells

CAR T-cell production was done as described [13,14]. Patients received the target CAR T-cell dose of 1×10^6/kg

Table 1
Patients' and Disease characteristics

Patients	
Total, no.	73
Age, median (range)	49 (20-73)
Gender	
Male	45 (61.6%)
Female	28 (38.4%)
KPS	
90%-100%	54 (74%)
70-80%	11 (15.1%)
50%-60%	4 (5.5%)
30%-40%	3 (4.1%)
Missing	1 (1.4%)
Histological subtype	
DLBCL NOS, de novo	28 (38%)
Transformed DLBCL (including Richter transformation)	22 (30%)
PMBCL	12 (16%)
High-grade B-cell lymphoma (DHL/NOS)	7 5/2 (9%)
MCL	4 (5%)
History of CNS involvement	
Yes	6 (8.2%)
No	67 (91.8%)
Previous ASCT	
Yes	25 (34.2%)
No	48 (65.8%)
Previous allo-SCT	
Yes	4 (5.5%)
No	69 (94.5%)
Bulky disease at time of apheresis	
Yes	12 (16.4%)
No	61 (83.6%)
Number of previous treatment lines	
2	27 (37%)
3 or more	46 (63%)
Stage at apheresis	
I/II	19 (26%)
III/IV	53 (72.6%)
No evidence of disease	1 (1.4%)
Disease status at apheresis	
CR	1 (1.4%)
PR	9 (12%)
SD/PD	63 (86%)
Primary refractory	
Yes	37 (51.4%)
No	35 (48.6%)

KPS indicates Karnofsky performance status; DLBCL, diffuse large B-cell lymphomas; PMBCL, primary mediastinal B-cell lymphoma; MCL, Mantle cell lymphoma; DHL, double hit lymphoma; CNS, central nervous system.

except for 1 patient who received 0.6 $\times$ 10^6/kg CAR T-cells because of insufficient production. Sixty-six (92%) patients did not receive any bridging therapy whereas 6 (8%) did receive therapy. The protocols used were gemcitabine, dexamethasone, and cisplatin (N = 1); bendamustine and polatuzumab (N = 2); reduced-dose cytoxan, adriamycin, oncovin, and prednisone (N = 1); etoposide, solumedrol, high dose ara-c, and cisplatin (N = 1); and mesna, ifosfamide, mitoxantrone, and etoposide (N = 1). Median time from apheresis to infusion was 10 days (IQR 10-11).

Table 2
Toxicity and Treatment

Toxicity	N = 73 (%)
CRS	62 (85)
Maximal grade	
1	47 (64)
2	8 (11)
3	5 (7)
4	2 (3)
Time from infusion (d), median (range)	4 (2-5)
Duration (d), median (range)	5 (4-9)
Treatment	12 (13)
Tocilizumab	5 (7)
Tocilizumab + steroids	4 (6)
ICANS	29 (40)
Maximal grade	
1	9 (12)
2	4 (6)
3	12 (16)
4	4 (6)
Time from infusion (d), median (range)	7 (6-9)
Duration (d), median (range)	4 (2-7)
Treatment	29 (40)
Steroids	6 (8)
Anti-epileptics	7 (10)
Steroids + anti-epileptics	16 (22)

Toxicity

Toxicity profile and treatment are presented in Table 2. CRS was observed in 62 patients (85%). Forty-seven (64.4%) had grade I CRS, 8 (11%) had grade II, 5(6.8%) had grade III and 2 (2.7%) had grade IV. Median time from CAR T-cell infusion to CRS was 4 days (IQR 2-5 days) and median duration of CRS was 5 days (IQR 4-9 days). Sixty-four (87.7%) patients did not require any treatment for the CRS, 5 (6.8%) received tocilizumab, and 4 (5.5%) were treated with tocilizumab and corticosteroids. ICANS was observed in 29 patients (39.7%) after a median of 7 days from CAR T-cell infusion (IQR 6-9 days). ICANS grade was 1 in 9 (12.3%), 2 in 4 (5.5%), 3 in 12 (16.4%) and 4 in 4 (5.5%). Median duration of ICANS was 4 days (IQR 2-7 days) and 16 (21.9%) patients required treatment with steroids.

Severe neutropenia (<0.5k/microliter) was observed in 62 patients (85%). First wave was captured in 53 (73%) patients at a median of 7 days post-CART-cell infusion (range −3 to 196). The median duration of the first wave was 9 days (IQR 6-14, range 1-39). Second wave of neutropenia was observed in 9 (12%) patients, with a median time of 38 days, (IQR 31-76, range 20-116). Its median duration was 5 days (IQR 3-8, range 1-34).

Notable adverse events that were captured during the first 28 days after infusion were as follows: 1 spleen rupture probably due to disease progression in a patient with primary mediastinal B-cell lymphoma, 1 perforation of duodenal ulcer, and 3 cases of death from disease progression. There were no cases of death that were attributed to CAR T-cell treatment.

Outcome

Response

Response data were evaluable for 72 patients, one patient deceased prior to his first response assessment. Overall response at day 28 was observed in 45 patients (62.5%). CR

Table 3
Response

	N = 72 (%)
ORR (CR + PR)	45 (62.5)
CR	27 (37.5)
PR	18 (25)
SD/PD	27 (37.5)

Overall response 28 days after CAR T-cell infusion.

was 37.5% (n = 27), and PR was 25% (n = 18). Stable or progressive disease (SD/PD) was reported in 27 (37.5%) patients (Table 3). The patient who received CAR T-cells in a dose lower than the target of 1×10^6/kg achieved CR 28 days after infusion without evidence of PD at data cut-off. Best response was CR in 28 patients (38.9%), PR in 17 (23.6%), and SD/PD in 27 (37.5%) Figure 1A presents the disease status pre-CAR T-cell therapy and at day 28. In univariate and multivariate regression analysis, we did not find any correlation between age, performance status, stage, bulky disease, lactate dehydrogenase (LDH), number of previous treatment lines, refractoriness, and disease status in apheresis to outcome or risk of toxicity. The response at day 28, as well as the best response, in patients with RT was CR in 4/8 and PD in 4/8. Among the 4 patients in CR, 2/4 were consolidated with alloSCT, and the other 2 did not receive further therapy. Neither of these 4 patients progressed after CAR T-cell therapy.

Survival

Median follow-up is 18 months (11.7-23). Median PFS and OS were 3.7 (2.2-NA) and 12.1 (8.7-NA) months, respectively (Figure 1B, C). Land mark analysis included patients that achieved their first response assessment demonstrated median OS of 15.5 months with superior OS to the patients that achieved CR/PR compared to those with SD/PD (1-year OS 67.2% versus 21.3%, Figure 1D). Twenty-eight patients (32%) died because of disease progression and 6 (8%) because of stem cell transplantation complications. In univariate and multivariate analysis the factors that were found to predict OS were response (CR/PR HR = 0.2 [0.096-0.448], $P = 6.40^{*}10^{-05}$), and bulky disease (>10 cm) (HR = 2.9 (1.301-6.584), $P = .009$). Duration of response (DOR) was 65.1% at 1 year and was significantly better for patients who achieved CR (Figure 1E). Five of the 8 patients with RT were alive at last follow-up. Among these patients 3 of them were in CR at day 28. One of the 4 patients who achieved CR in day 28 deceased later because of alloSCT complications.

Consolidation with alloSCT after CAR T-cell treatment

AlloSCT as consolidation after CAR T-cell therapy was performed in 15/73 (20%) of the patients. In the initial study period (first 1.5 years) alloSCT was done per protocol for 12 patients who achieved response to CAR T-cell therapy and later on to relapsed or nonresponding patients. Transplant characteristics and complications are presented in Table 4. Six patients (40%) were in CR, and 9 (60%) were in PR after the

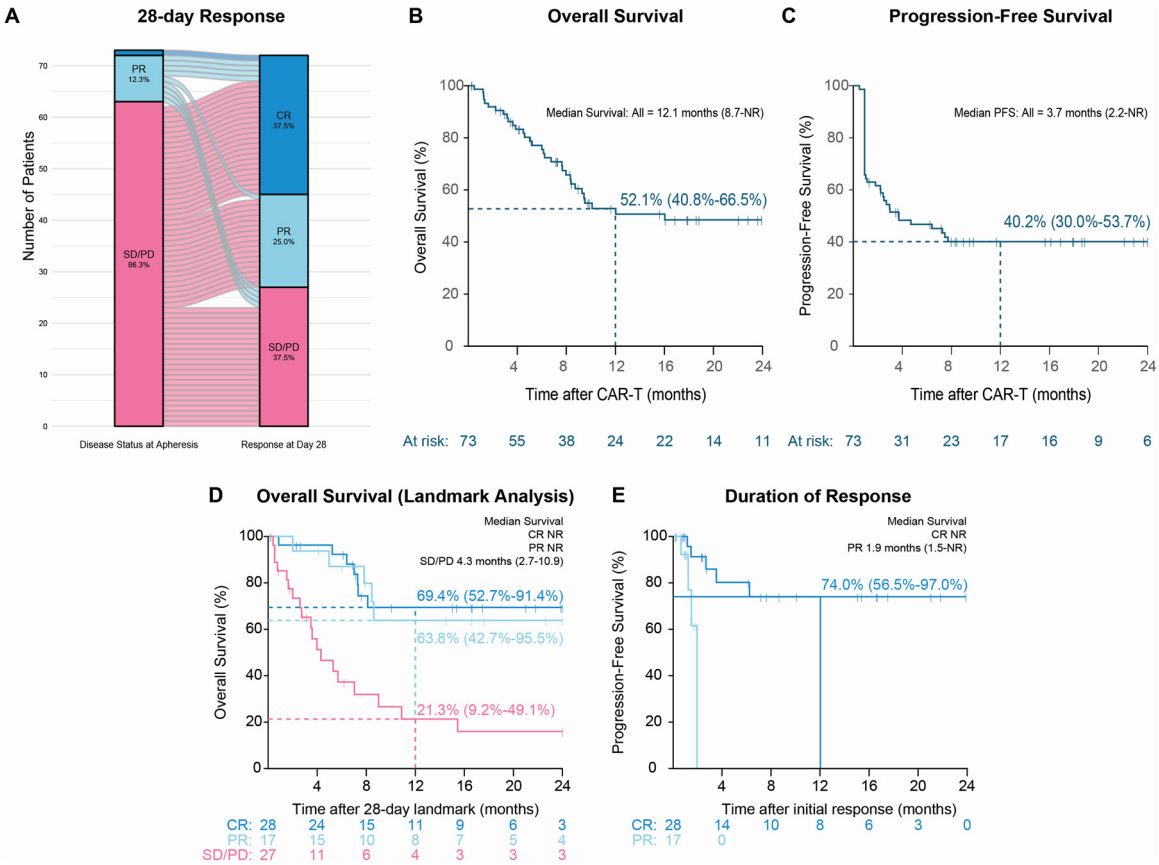

Figure 1. Response and Survival outcomes of the study population. (A) Alluvial plot describing disease status at apheresis and at day 28. Most of the patients achieved PR or CR. (B) Overall survival of the study population—1-year OS of 52.1%. (C) Progression-free survival of the study population—1-year PFS of 40%. (D) Landmark analysis of the patients that reached their first imaging evaluation pot CAR T-cell infusion. OS is significantly better in the patients that achieved CR or PR versus SD/PD. (E) Duration of response significantly better in the patients that achieved CR versus PR.

Table 4
Allo-SCT Characteristics

All	N = 15 (%)
Disease status after CAR T-Cell	
CR	6 (40)
PR	9 (60)
Disease status at transplantation	
CR	5 (33)
PR	7 (47)
PD	3 (20)
Donor type	
Matched sibling	6 (40)
Matched unrelated	7 (47)
Haploidentical	2 (13)
Disease	
DLBCL	10 (67)
PMBCL	2 (13)
Richter	2 (13)
DHL	1 (7)
GVHD	
Acute	5 (33)
Chronic	1 (6)
Response	
CR	9 (60)
PR	4 (27)
PD	1 (6)
Not evaluable	1 (6)
Death	
Disease related	4
AlloSCT related	3

GVHD indicates graft-versus-host disease.

CART-cell therapy. The median time to alloSCT was 60 days (range 48-130) after cell infusion. PD was identified by repeated PET/CT done before alloSCT in 3 (20%) of the patients who responded initially to CAR T-cell therapy. Six patients (40%) had matched sibling donors, 7 (47%) had matched unrelated donors, and 2 (13%) had haploidentical donors. Five patients (53%) had acute graft-versus-host disease, and 1 had chronic graft-versus-host disease. As evident in the swimmer plot (Figure 2), a total of 8 patients are still alive. Among the 6 patients with complete response after CAR T-cell therapy, 3 died, 1 of PD and 2 because of transplant-related toxicity. Of the 9 patients with PR post CAR T-cell therapy, 4 converted to CR after transplantation and 4 died, all of PD, including 2 patients who converted to CR after transplantation. The sequence of events for the patients who underwent alloSCT is presented in Figure 2.

DISCUSSION

CAR T-cell therapy revolutionized the treatment of relapsed/refractory (R/R) ABCL. In the pre CAR T-cell era, patients with R/R ABCL, who were unable to undergo an ASCT or whose disease progressed after ASCT, were mostly treated with palliative care and had dismal overall survival [20]. The long-term survival for patients treated with commercial CAR T-cells after at least 2 lines was consistently reported as 35% to 40% [4,5,21,22].

Our study describes a cohort of 73 patients treated with an academic local CAR T-cell product that includes a CD28 costimulatory domain [13,14]. The production efficiency was 98.6%, and all the screened patients were eventually treated with CAR T-cells. The local production and the short vein-to-vein turnover time (10 days) enabled us to avoid bridging therapy in most patients and to include patients who had rapidly

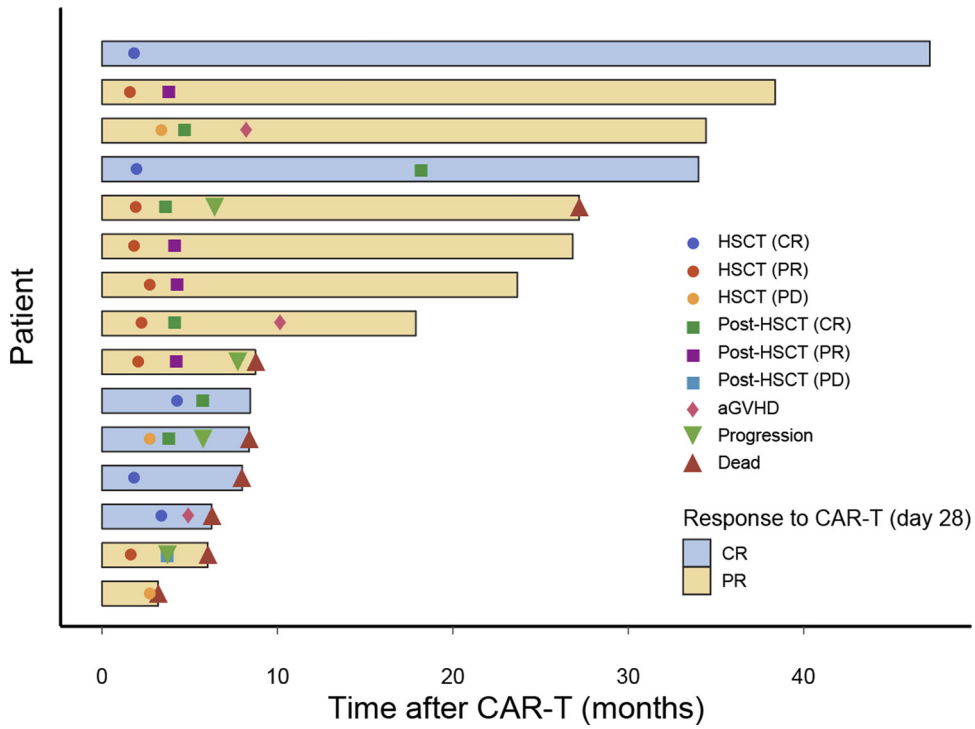

Figure 2. Swimmer plot of the 15 patients who underwent allo-SCT after CAR T-cell therapy. Six patients achieved CR and 9 PR after CAR T-cell therapy. Seven patients died after transplantation, 3 of whom had achieved CR after CAR T-cell therapy.

progressing disease. Compared to the main 3 pharma-sponsored trials (ZUMA-1, Juliet, and TRANSCEND NHL 001), we had a younger patient population (median age was 49 years) but more patients with primary refractory disease (50.7%) [4,5,22]. ORR and median PFS in our study are slightly lower, but long-term PFS and OS are very similar to those reported in the literature. The relative lower ORR and median PFS can be explained by the study population, which included patients with rapidly progressing disease and patients with expected poor prognosis such as RT and high-grade B-cell lymphoma.

As in our analysis, the real-world experience with Axi-cel demonstrated a slightly lower response rate than ZUMA-1 [23,24]. The real-world experience with Tisa-cel demonstrated similar response rates, albeit in a significantly smaller cohort of patients [23,25].

When the first CAR T-cell products were approved for clinical use, many health care professionals were discouraged because of the financial toxicity of this procedure [26–28]. The cost effectiveness is still not clear. The fact that CAR T-cell therapy may cure only 35% to 40% of patients with R/R diffuse large B-cell lymphoma means that 60% of them could have received other, significantly cheaper, salvage therapies that would also prolong their lives but not cure them [29]. The point-of-care production is not only faster but also potentially cheaper because it reduces the costs of shipment and bridging chemotherapy. Because currently we are lacking robust tools to predict response to CAR T-cell therapy, lowering the costs of the procedure is extremely important.

We and others demonstrated that achievement of CR predicts better OS [4,5,22]. Whereas others found LDH and tumor mass to predict response rate [4,5,22], we could not find any significant clinical predictors of response to CAR T-cell treatment [23,30]. Higher grades of CRS or ICANS were also not predictive. The small sample size can explain the difference.

AlloSCT after CAR T-cell therapy for responding patients is debatable [16]. During the first 1.5 years of the study period, we recommended alloSCT to all patients who responded to CAR T-cell therapy, and after this period alloSCT was suggested according to physician discretion. In this cohort, a total of 15 responding patients underwent alloSCT as consolidation. Seven patients died after alloSCT, 2 patients in CR because of transplant complications, and 5 because of progressive disease. Considering the relatively small numbers of patients treated with consolidative alloSCT after CAR T-cell therapy, based on the current analysis, it appears that this approach did not benefit, and in the meantime, it is generally discouraged.

To summarize, we present the outcome of 73 patients with ABCL who were treated with locally produced CAR T-cell therapy. The point-of-care production made the turnover time much faster and saved shipment and bridging therapy costs. Taking into consideration the amendment made in the age inclusion criteria and the change of alloSCT referral policy in the course of the trial, the long-term outcomes are comparable to those reported with the commercial products. Consolidative alloSCT post CAR T-cell therapy, which was done initially per protocol for 15 responsive patients, did not appear to be beneficial.

ACKNOWLEDGMENTS

Financial disclosure: Supported by the Memorial Sloan Kettering Cancer Center Core grant (P30 CA008748) from the National Cancer Institute/National Institutes of Health (S.C.). R. S. serves as a consultant for Medexus and MyBiotics.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: M.B., E.J., and A.N. contributed to study design. All authors contributed to data analysis and manuscript preparation.

REFERENCES

1. Hagberg H, Gisselbrecht C, CORAL study group. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. *Ann Oncol*. 2006;17(suppl 4). iv31-iv32.
2. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:4184–4190.
3. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. *N Engl J Med*. 2018;379:64–73.
4. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol*. 2019;20:31–42.
5. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380:45–56.
6. 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;126:2123–2138.
7. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant*. 2019;54:1643–1650.
8. Sermer D, Batlevi C, Lia Palomba M, et al. Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies. *Blood Adv*. 2020;4:4669–4678.
9. Jalbert JJ, Arnason JE, Ge W, et al. Real-world treatment patterns among patients with diffuse large B-cell lymphoma (DLBCL) treated with CD19-directed chimeric antigen receptor T-cell therapy (CAR T). *J Clin Oncol*. 2020;38(15_suppl):e19351.
10. Hu Y, Tan Su Yin E, Yang Y, et al. CAR T-cell treatment during the COVID-19 pandemic: management strategies and challenges. *Curr Res Transl Med*. 2020;68:111–118.
11. Ortiz de Landazuri I, Egri N, Muñoz-Sánchez G, et al. Manufacturing and management of CAR T-cell therapy in "COVID-19's time": central versus point of care proposals. *Front Immunol*. 2020;11: 573179.
12. Ghorashian S, Kramer AM, Onuoha S, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. *Nat Med*. 2019;25:1408–1414.
13. Jacoby E, Bielorai B, Avigdor A, et al. Locally produced CD19 CAR T cells leading to clinical remissions in medullary and extramedullary relapsed acute lymphoblastic leukemia. *Am J Hematol*. 2018;93:1485–1492.
14. Itzhaki O, Jacoby E, Nissani A, et al. Head-to-head comparison of in-house produced CD19 CAR-T cell in ALL and NHL patients. *J Immunother Cancer*. 2020;8:(1) e000148.
15. Avigdor A, Shouval R, Jacoby E, et al. CAR T cells induce a complete response in refractory Burkitt Lymphoma. *Bone Marrow Transplant*. 2018;53:1583–1585.
16. Bouziana S, Bouzianas D. Exploring the dilemma of allogeneic hematopoietic cell transplantation after chimeric antigen receptor T cell therapy: to transplant or not? *Biol Blood Marrow Transplant*. 2020;26(8): e183–e191.
17. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068.
18. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25:625–638.
19. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103:275–282.
20. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematol Am Soc Hematol Educ Program*. 2011;2011(1):498–505.
21. Yassine F, Iqbal M, Murthy H, Kharfan-Dabaja MA, Chavez JC. Real world experience of approved chimeric antigen receptor T-cell therapies outside of clinical trials. *Curr Res Transl Med*. 2020;68:159–170.
22. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396 (10254):839–852.
23. Vitale C, Strati P. CAR T-cell therapy for B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia: clinical trials and real-world experiences. *Front Oncol*. 2020;10:849.
24. Nastoupil LJ, Jain MD, Spiegel JY, et al. Axicabtagene Ciloleucel (Axi-cel) CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: real world experience. *Blood*. 2018;132(Suppl 1). 91-91.
25. Jaglowski S, Hu Z-H, Zhang Y, et al. Tisagenlecleucel chimeric antigen receptor (CAR) T-cell therapy for adults with diffuse large B-cell

lymphoma (DLBCL): real world experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry. *Blood*. 2019;134(Suppl 1). 766-766.

26. Baumgardner JR, Brauer MS, Zhang J, et al. CAR-T therapy and historical trends in effectiveness and cost-effectiveness of oncology treatments. *J Comp Eff Res*. 2020;9:327–340.
27. Chicaybam L, Bonamino MH, Invitti AL, et al. Overhauling car t cells to improve efficacy, safety and cost. *Cancers (Basel)*. 2020;12(9):1–26.
28. Lin JK, Muffly LS, Spinner MA, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma. *J Clin Oncol*. 2019;37:2105–2119.
29. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2020;38:155–165.
30. Vercellino L, Di Blasi R, Kanoun S, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. *Blood Adv*. 2020;4:5607–5615.