Safety and efficacy of allogeneic anti-CD19 chimeric antigen receptor T cells (CAR-T cells) in persons with CD19-positive B-cell acute lymphoblastic leukemia (B-ALL) relapsing after an allotransplant remain unclear. Forty-three subjects with B-ALL relapsing post allotransplant received CAR-T cells were analyzed. 34 (79%; 95% confidence interval [CI]: 66, 92%) achieved complete histological remission (CR). Cytokine release syndrome (CRS) occurred in 38 (88%; 78, 98%) and was ≥ grade-3 in 7. Two subjects died from multiorgan failure and CRS. Nine subjects (21%; 8, 34%) developed ≤ grade-2 immune effector cell-associated neurotoxicity syndrome (ICANS). Two subjects developed ≤ grade-2 acute graft-versus-host disease (GvHD). 1-year event-free survival (EFS) and survival was 43% (25, 62%). In 32 subjects with a complete histological remission without a second transplant, 1-year cumulative incidence of relapse was 41% (25, 62%) and 1-year EFS and survival, 59% (37, 81%). Therapy of B-ALL subjects relapsing post transplant with donor-derived CAR-T cells is safe and effective but associated with a high rate of CRS. Outcomes seem comparable to those achieved with alternative therapies but data from a randomized trial are lacking.

Introduction

Persons experiencing B-cell acute lymphoblastic leukemia (B-ALL) relapse after an allogeneic hematopoietic cell transplant are typically treated by stopping immune
suppression, receiving a donor lymphocyte infusion (DLI) and/or receiving a second transplant from the same or a different donor. The outcomes of these interventions are unsatisfactory [1–3].

Autologous anti-CD19 chimeric antigen receptor T cells (CAR-T cells) are an effective therapy for advanced CD19-positive B-ALL, often followed by an allotransplant [4–8]. Cumulative incidence of relapse (CIR) and event-free survival (EFS) of persons receiving CAR-T cells without an allotransplant are typically short [9]. Allogeneic anti-CD19 CAR-T cells receive activation signals from T-cell receptors (TCRs) to target cell alloantigens and from CD19 on leukemia cells. This dual signaling may increase the anti-leukemia efficacy compared with autologous CAR-T cells. Allogeneic anti-CD19 CAR-T cells can be developed from donor T cells in allotransplant recipients who relapse. However, the safety and efficacy of this approach are unknown.

We determined the safety and efficacy of donor-derived anti-CD19 CAR-T cells in 43 subjects with CD19-positive B-ALL relapsing after an allotransplant. Outcomes from data reported in this setting with DLI and with a second allotransplant were then compared. Results of donor-derived anti-CD19 CAR-T cells seem at least comparable if not better than these alternatives. However, these results can be tested only in a randomized trial.

**Methods**

**Subjects and data collection**

Forty-three subjects with CD19-positive B-ALL who received an allotransplant, had a bone marrow relapse and received donor-derived anti-CD19 CAR-T cells from July 2015 to March 2019 were enrolled. Major inclusion criteria included (1) Eastern Cooperative Oncology Group performance score ≤grade-2; (2) estimated survival >3 months; (3) no prior acute graft-versus-host disease; and (4) refusal to receive a second allotransplant. Posttransplant relapse was defined as >5% bone marrow blasts or a positive measurable residual disease (MRD) test after ≥2 prior post-transplant MRD tests. Details of MRD testing are reported [6, 8]. Data were extracted from the electronic medical records of subjects enrolled in ChiCTR-OOC-16008447, protocol number: ChIECRCT-20160022 and ChiCTR-OIC-17012374, protocol number: XYFY2017-KL033-01. The study was approved by the Ethics Committee of the Army Medical University.

**CD19-targeting CAR-T manufacturing**

The method for obtaining anti-CD19 CAR-T cells is previously described [7]. Briefly, blood mononuclear cells were obtained from transplant donors by leukapheresis, T cells were purified and transfected with lentivirus containing sequence expressing chimeric antigen receptors (CARs) with the 4-1BB or CD28 intracellular domain as co-stimulation signal and expanded in vitro. Quality control was based on the Chinese Pharmacopoeia (2015 Version), which includes viability >70% (Fig. 1).

**CD19-targeting CAR-T cell therapy**

Three preinfusion immune suppressive regimens were: (1) regimen 1: fludarabine, 30 mg/mE + 2/day for 2–4 days and cyclophosphamide, 200 mg/mE + 2/day for 2 days; (2) regimen 2: fludarabine, 30 mg/mE + 2/day for 3 days,
cyclophosphamide, 350 mg/mE + 2/day for 2 days and cytarabine, and 100 mg/mE + 2/day for 4 days; and (3) regimen 3: cyclophosphamide, 500 mg/mE + 2/day for 3 days. Overall, 34 subjects received regimen 1. Regimen 2 was given to five younger subjects with many leukemia cells. Regimen 3 was given to four older subjects with few leukemia cells. Expansion and persistence of CAR-T cells were analyzed by flow cytometry or by CAR-T cell DNA copy number [7]. Median dose of infused CAR-T cells was 1.76 × 10E + 6/kg (range, 0.4–12 × 10E + 6/kg).

Response assessment

Complete remission was defined by histology (≤5% bone marrow blasts) and a negative MRD test (≤0.01% bone marrow blasts) assessed by multiparameter flow cytometry to detect the leukemia-associated profile [8, 10]. It also included normal maturation of all cell components in the bone marrow, no extramedullary leukemia (e.g. central nervous system, testes or soft tissue), blood neutrophil concentration ≥1 × 10E + 9/L, blood platelet concentration ≥100 × 10E + 9/L and RBC and platelet transfusion independence.

Relapse included histologic and a positive MRD test. Histologic relapse was defined as blasts ≥5% in blood or bone marrow and/or in an extramedullary site after achieving a complete histologic remission post transplant. Molecular relapse was defined as a positive MRD test (≥0.01% and ≤5%) without evidence of histologic relapse post transplant [11].

Adverse events

Grading of acute GvHD was based on published criteria [12, 13], as was grading of cytokine release syndrome (CRS) [14]. Immune effector cell-associated neurotoxicity syndrome (ICANS) was graded using the Common Terminology Criteria for Adverse Events [15]. CRS, ICANS, and acute GvHD were managed as previously described [7, 14, 15].

Statistics

The time of CAR-T cell transfusion was used as the origin in all the time-to-event analyses. Analysis of CIR used relapse as the event. For analysis of EFS, no response, relapse or death, whichever occurred first, was regarded as the event. In survival analyses, death was the event. Subjects without an event were censored at the date they were last known to be alive. Two subjects receiving a second allotransplant were censored at the time of second transplant. The primary study endpoints were safety and efficacy. Secondary endpoints were covariates associated with safety and efficacy. Data were analyzed as of September 30, 2019 with a median follow-up of survivors of 17 months (range, 6–47 months).

The chi-square statistic or Fisher exact test was used for comparisons between categorical variables, and the Mann–Whitney U test was used for continuous variables. The Kaplan–Meier method was used to calculate the probability of EFS and survival. P values were two-sided, and P < 0.05 was considered significant. SPSS statistical software for Windows, version 24.0 (SPSS, Chicago, IL, USA) was used for statistical analyses.

Results

Subjects

Forty-three subjects were enrolled and analyzed (Table 1). Twenty-nine were male. Median age was 24 years (range, 4–60 years). Pretransplant conditioning regimens are displayed in Table 1. Donors were HLA-identical siblings (N = 17) or HLA-haploypotype-matched relatives (N = 26). Bone marrow blasts at relapse were 0.01–5% in 13 subjects, 5–50% in 20 and >50% in 10 subjects. The median interval from relapse to CAR-T cell infusion was 42 days (range, 35–59 days). Postrelapse therapies included stopping immune suppression (N = 12), DLI (N = 7), chemotherapy (N = 19), and DLI and chemotherapy (N = 5; Supplementary Table 1).

Overall, 18 subjects received CD19–28z CAR-T cells and 25, CD19-BBz CAR-T cells. Pre infusion, 34 subjects (79%) received regimen 1, 5 regimen 2, and 4, regimen 3. Median numbers of infused CAR-T cells were 1.76 × 10E + 6/kg (range, 0.4–12 × 10E + 6/kg; Table 1).

Safety

All subjects had a decreased concentration of hemoglobin, WBCs, neutrophils, lymphocytes, and platelets. One subject had an increased activated partial thromboplastin time. Two subjects had an increased alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactic dehydrogenase levels.

CRS of any grade developed in 38 subjects (88%; 95% confidence interval (CI), 78, 98%) and was ≥grade-3 in 7 subjects. Six of seven subjects with ≥grade-3 CRS had bone marrow blasts ≥5% including four with bone marrow blasts ≥50% and two, 20–50%. There was no significant correlation between risk of severe CRS or incidence or severity of ICANS and percentage bone marrow blasts. Overall, 16 of 18 subjects receiving CD19–28z CAR-T cells developed CRS, severe in 5. 22 of 25 subjects receiving CD19-BBz CAR-T cells developed CRS, severe...
in 4. 3 of 18 subjects receiving CD19-28z CAR-T cells developed ICANS compared with 6 of 25 receiving CD19- 
BBz CAR-T cells (P = 0.79). Two subjects receiving CAR-
T cells developed < grade-2 acute GVHD. Nine subjects
(21% [8, 34%]) developed grade-1/2 ICANS with none
≤ grade-3.

### Efficacy

41 subjects survived ≥21 days and were evaluable for response. Two died in <21 days from CRS and multiorga
n failure on days 14 and 21 and were included in the intent-to-
treat analysis. 34 subjects (79% [66, 92%]) achieved a
complete histological remission including 12 of 13 with
0.01–5% bone marrow blasts and a positive MRD test, 14
of 20 with 5–50% bone marrow blasts and 8 of 10 with
≥50% bone marrow blasts. Although there are no significant
differences in rates between the cohorts, the comparison is
not adjusted for other covariates such as the preinfusion
regimen or type of CAR-T cells. 14 of 18 subjects receiving
CD19–28z CAR-T cells achieved a complete histological remi-
session compared with 20 of 25 receiving CD19-BBz
CAR-T cells. Because therapy assignment was not random
and not adjusted for other covariates, we did not compare
these rates statistically.

The 34 subjects achieving a complete histological remission received different CAR-T doses, including two
of four receiving <1 × 10^6, 23 of 26 receiving 1–2 ×
10^6, and 9 of 13 receiving >2 × 10^6. Because therapy assignment was not random, we did not compare
these rates statistically. These 34 received different pre-
infusion regimens, including 26 receiving regimen 1, five of
five receiving regimen 2, and three of four receiving regimen 3.

1-year probabilities of EFS and survival were 43% (25,
62%; Fig. 2a, b). 1-year probability of CIR was 41% (25,
62%) in subjects achieving a complete histological remi-
session not receiving a second transplant (Fig. 2c). In the
32 subjects achieving a complete histological remission not
receiving a second transplant 1-year probabilities of EFS
and survival were 59% (37, 81%; Fig. 2d, e). Two of nine
subjects not achieving a complete histological remission lost
CD19 expression. Three other subjects who relapsed
lost CD19 expression.

### CAR-T cell dynamics

CAR-T cell numbers peaked on day 9 (range, day 3–61)
after CAR-T cell infusion in the 36 subjects with complete
data. Median interval of detectable blood CAR-T cells
post infusion was 89 days (range, 10–1230 days). Post-
infusion CAR-T cells peaked on day 10 (range, days 3–61) and 9 (range, days 7–21) in subjects with and
without a complete histological remission, respectively.
Corresponding median postinfusion intervals of detect-
able blood CAR-T cells were 118 days (range, 10–1230 days) and 21 days (range, 14–28 days). Median
peak concentration was 4.85 × 10^5/L (range, 0.14–1.18 × 10^5/L). Median peak percentage of all
cells was 23% (range, 2–65%).

### Table 1 Patient covariates (N = 43).

| Variable                                      | Value          |
|-----------------------------------------------|----------------|
| Male                                          | 29             |
| Age (Median; range)                           | 24 (4–60)      |
| Donor                                         | 26             |
| HLA-identical sibling                         | 17             |
| HLA-haplotype-matched                         | 26             |
| Graft                                         | 17             |
| Blood                                         | 17             |
| Blood and bone marrow                         | 26             |
| BCR/ABL1 positive                             | 5              |
| No                                            | 38             |
| Cyto genetics                                  | 14             |
| Abnormal                                      | 29             |
| Normal                                        |                |
| Mutation                                      | 23             |
| Yes                                           | 20             |
| No                                            |                |
| Transplant conditioning regimen               | 17             |
| BU/CY                                         | 26             |
| BU/CY/Ara-C/CCNU                              |                |
| Posttransplant immune suppression             | 17             |
| CSA/MMF/MTX                                   | 26             |
| Tacrolimus/MMF/ATG/MTX                        |                |
| Interval from transplant to relapse (mo; median; range) | 1 (1–25) |
| Interval from relapse to CAR-T (d; median; range) | 42 (35–59) |
| Therapy for relapse                           | 12             |
| Stop immune suppression                       | 7              |
| DLI                                           | 19             |
| Chemotherapy                                  | 5              |
| Chemotherapy/DLI                              |                |
| Bone marrow blasts pre infusion               | 13             |
| 0.01-(MRD-positive)                           | 20             |
| 5–50%                                         | 10             |
| >50%                                          |                |
| Co-stimulatory molecular                      | 18             |
| CD28                                          | 25             |
| 4–1BB                                         |                |
| Preinfusion therapy                           | 34             |
| Regimen 1                                     | 5              |
| Regimen 2                                     | 4              |
| Regimen 3                                     |                |
| CAR-T cell dose (×10^6/kg; median; range)      | 1.76 (0.4–12)  |
| <1                                            | 4              |
| 1–2                                           | 26             |
| >2                                            | 13             |

*HLA* human leukocyte antigen, *BU* busulfan, *CY* cyclophosphamide, *Ara-C* cytarabine, *CCNU* lomustine, *CSA* cyclosporine, *MMF* mycophenolate mofetil, *MTX* methotrexate, *ATG* anti-thymocyte globulin, *MRD* measurable residual disease, *DLI* donor lymphocyte infusion.
Discussion

Our data indicate that donor-derived anti-CD19 CAR-T cells are a safe and effective therapy for B-ALL recurrence after allotransplantation. Adverse effects of CAR-T cell therapy are mainly CRS and ICANS, severity of which reportedly correlates with cancer volume, preinfusion regimen and CAR-T cell dose in some but not all studies [16, 17]. We found no such correlations but we had relatively few subjects and many confounding covariates. Others have reported similar data [18, 19]. Although the incidence of CRS in our study is highly compared with studies of autologous CAR-T cells, most cases were low-grade and controllable. Absent a randomized comparison any conclusion is tentative. Nine subjects developed grade-1/2 ICANS with none ≥grade-3. This rate is like that reported after autologous CAR-T cell therapy [20].

Donor-derived CAR-T cell treatment can potentially cause acute GvHD. In a mouse model, donor-derived CAR-T cells had little GvHD but a potent graft-versus-leukemia (GvL) effect [21]. A systematic review reported a low risk of acute GvHD after allogeneic CAR-T cells [22]. Two subjects in our study developed mild acute GvHD. These data imply an ability to separate GvHD from GvL, albeit in an artificial setting.

There are a few reports of using allogeneic CAR-T cells to treat B-cell cancers after an allogeneic hematopoietic stem cell transplant (Table 2) [18, 23–29]. No study had

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Table 2 Reports of donor CAR-T cells given for relapse of B-cell cancers after an allotransplant.

| Subjects (N) | Age (y) | B-ALL | T-ALL (CD19+) | B-CLL | Lymphoma | Ref. |
|-------------|---------|-------|---------------|-------|----------|------|
| 8           | 32 (9–59) | 2     | 2             | 4     |          | [23] |
| 10          | 52 (44–66) | 2     | 2             | 4     | 2        | [24] |
| 16          | 50 (23–74) | 2     | 12            | 4     |          | [25] |
| 9           | 39 (15–64) | 5     | 4             | 4     |          | [26] |
| 20          | 46 (20–68) | 1     | 4             | 5     | 5        | [27] |
| 26          | 40 (21–61) | 17    | 1             | 4     | 3        | 1    | [28] |
| 30          | 14 (5–60)  | 2     | 27            | 1     |          | [29] |
| 6           | 27 (8–44)  | 1     | 5             | 5     |          | [18] |

Ph+ Philadelphia-chromosome, BCRABL1 qRT-PCR result, Ref reference.

*aYears (y); median; range.
Table 3 Therapies of relapse of ALL post allotransplant.

| N   | ALL | Agea | CR | Stop immune suppressionb | CIR | EFS  | Survival | aGvHD ≥ grade 2 | Ref. |
|-----|-----|------|----|--------------------------|-----|------|----------|----------------|------|
|     | B   | T    |    |                          |     |      |          |                |      |
| This study | 43  | 43   | 24 (4-60) | 79%  | 57% | 43%  | 43% | 0 |  |
| DLI  | 10  | -    | 11 (< 1-25) | - | N/A | N/A  | N/A | N/A | [30] |
| DLI  | 30  | -    | 21 (10-52) | 25% | N/A | N/A  | N/A | 5% | N/A | [31] |
| DLI  | 8   | -    | 24 (18-39) | - | 5  | 2-14 | N/A | - | 5 | [32] |
| DLI  | 10  | -    | 33 (18-40) | 70% | N/A | N/A  | N/A | - | 6 | [33] |
| Second transplant | 245 | 186 | 59 | 35 (18-74) | N/A | N/A | 56% | 20% | 30% | 127 | [34] |
| Second transplant | 11  | -    | 41 (18-65) | N/A | Tapered at 3 mo | N/A | - | - | N/A | [35] |
| Second transplant | 214 | -    | 8 (1-18) | 78% | N/A | 44% | 34% | 43% | 53 | [36] |
| Second transplant | 27  | 22   | 5 | 37 (7-60) | N/A | N/A | 56% | 30% | 41% | 15  | [37] |
| Second transplant | 31  | -    | 26 (7-49) | 75% | N/A | N/A | N/A | 23% | 13 | [38] |

Estimates for studies with <30 subjects are unreliable with wide 95% confidence intervals so complete histological remission rates, CIR, EFS, and survival are not indicated.

CR complete histological remission, DLI donor lymphocyte infusion, EFS event-free survival, GvHD graft-versus-host disease, Ref reference, N/A not available.

*aYear; median range.

*bMonth; median range.

>30 subjects. Moreover, most subjects in these reports received a second transplant making critical analyses of safety and efficacy of the CAR-T cell infusion impossible. We censored data from subjects who received a second transplant, making it possible to ascertain the safety and efficacy of CAR-T cell therapy alone.

Other potential therapies of relapse after an allotransplant include stopping immune suppression, receiving DLI and/or receiving a second transplant from the same or a different donor. We summarize the data using these strategies in Table 3. It was difficult to compare our outcomes with these other strategies. There are only four studies of DLI, three of which had ≤10 subjects. There were only five studies of a second transplant only two of which had many subjects and none indicated consecutive subjects. Studies of stopping posttransplant immune suppression were typically confounded by combination with other therapies, often given concurrently. These limited data and confounding factors make it impossible to critical compare our data with those from other studies. A randomized trial is needed to resolve this question but is highly unlikely.

Our study has important limitations. We had relatively few subjects who with different diagnoses received diverse postrelapse interventions before CAR-T cell therapy. They also received different preinfusion regimens, different CAR-T cell constructs and different doses which preclude us from making definitive conclusions regarding subject-, disease- and therapy-related covariates correlated with outcomes. Consequently, we refrained from comparing outcomes of covariates such as preinfusion regimen and type and dose of CAR-T cells. Results of such comparisons are likely to be confounded by known and latent (unknown) covariates and small sample sizes, are unreliable and are not statistically justifiable. Also, because our subjects are not consecutive cases of everyone relapsing at the study centers there are important selection biases. Our study was retrospective, and participating center admission records were not independently audited.

It should also be noted that, CAR-T cell manufacturing in different medical centers may cause heterogeneity, but every procedure complies with a rigorous quality control, which is consistent. The outcomes of our study with the largest number of relapsed ALL subjects are satisfactory, donor-derived CAR-T is a good choice for those who are not eligible for receiving a second transplant.

In summary, we show therapy of recurrent B-ALL after an allotransplant with donor-derived anti-CD19 CAR-T cells is safe and effective. Outcomes seem comparable to those achieved with alternative therapies. However, the relative safety and efficacy of these alternatives can be accurately determined only in a randomized trial.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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