Safety of allogeneic hematopoietic cell transplant in adults after CD19-targeted CAR T-cell therapy

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Key Points
- The toxicity of allo-HCT in patients with prior CAR-T therapy was not higher than what is expected in these high-risk patients.
- In ALL patients, there seems to be a benefit from earlier utilization of allo-HCT after CAR-T therapy.

Introduction

Treatment with autologous CD19-specific chimeric antigen receptor T-cell (CAR-T) therapy has shown promising efficacy in patients with relapsed or refractory acute lymphoblastic leukemia (ALL), B-cell non-Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL).1-6 Allogeneic hematopoietic cell transplantation (allo-HCT) is often offered to ALL patients to consolidate remission achieved after CAR-T therapy. In NHL/CLL, allo-HCT is primarily used in patients who have refractory disease after CAR-T therapy or relapse after an initial response if a subsequent remission is achieved with additional treatment.7,8 Lymphodepletion (LD) chemotherapy and CAR-T therapy have immunosuppressive and immunomodulatory effects, and their impact on the immune system and endothelium could affect the safety profile of allo-HCT.9,10 We report safety and toxicity data from patients undergoing allo-HCT after receiving CAR-T therapy.

Methods

Patients with ALL, NHL, or CLL who received CAR-T therapy on an investigator-initiated phase 1/2 clinical trial (NCT01865617)4-6 and subsequently underwent allo-HCT were included in this analysis.
| Table 1. Transplant characteristics in patients with prior CD19 CAR-T treatment |
|-------------------------------------------------|-----------------|-----------------|
| Age, median (range), y                          | 39 (23-74)      | 52 (37-65)      | 46 (23-74)      |
| Dose of first CAR-T therapy, cells/kg           |                 |                 |                 |
| $2 \times 10^5$                                 | 8 (42)          | 2 (15)          | 10 (31)         |
| $2 \times 10^6$                                 | 11 (58)         | 9 (70)          | 20 (63)         |
| $2 \times 10^7$                                 | 0 (0)           | 2 (15)          | 2 (6)           |
| LD regimen for first CAR-T therapy              |                 |                 |                 |
| Cy-Flu                                         | 16 (84)         | 10 (77)         | 26 (81)         |
| Cy-based without Flu                           | 3 (16)          | 3 (23)          | 6 (19)          |
| Best response to first CAR-T therapy *         |                 |                 |                 |
| CR                                             | 18 (95)         | 2 (15)          | 20 (62)         |
| PR                                             | 0 (0)           | 5 (39)          | 5 (16)          |
| SD                                             | 0 (0)           | 2 (15)          | 2 (6)           |
| PD                                             | 1 (5)           | 4 (31)          | 5 (16)          |
| CRS (grade) after first CAR-T therapy †        |                 |                 |                 |
| 0                                              | 7 (37)          | 3 (23)          | 10 (31)         |
| 1                                              | 4 (21)          | 5 (39)          | 9 (28)          |
| 2                                              | 7 (37)          | 4 (31)          | 11 (35)         |
| 3                                              | 1 (5)           | 1 (8)           | 2 (6)           |
| NT (grade) after first CAR-T therapy ‡         |                 |                 |                 |
| 0                                              | 12 (63)         | 5 (39)          | 17 (53)         |
| 1                                              | 1 (5)           | 2 (15)          | 3 (9)           |
| 2                                              | 2 (11)          | 4 (31)          | 6 (19)          |
| 3                                              | 4 (21)          | 2 (15)          | 6 (19)          |
| 4                                              | 0 (0)           | 0 (0)           | 0 (0)           |
| Second CAR-T infusion, n                       | 2               | 7               | 9               |
| Best response to second CAR-T therapy          |                 |                 |                 |
| CR                                             | 2 (100)         | 1 (14)          | 3 (34)          |
| PR                                             | 0 (0)           | 2 (28.5)        | 2 (22)          |
| SD                                             | 0 (0)           | 2 (28.5)        | 2 (22)          |
| PD                                             | 0 (0)           | 2 (28.5)        | 2 (22)          |
| CRS (grade) after second CAR-T therapy         |                 |                 |                 |
| 0                                              | 2 (100)         | 4 (57)          | 6 (67)          |
| 1                                              | 0 (0)           | 2 (29)          | 2 (22)          |
| 2                                              | 0 (0)           | 1 (14)          | 1 (11)          |
| 3                                              | 0 (0)           | 0 (0)           | 0 (0)           |
| NT (grade) after second CAR-T therapy          |                 |                 |                 |
| 0                                              | 2 (100)         | 5 (72)          | 7 (77)          |
| 1                                              | 0 (0)           | 0 (0)           | 0 (11)          |
| 2                                              | 0 (0)           | 1 (14)          | 1 (11)          |
| 3                                              | 0 (0)           | 0 (0)           | 0 (0)           |
| 4                                              | 0 (0)           | 1 (14)          | 1 (11)          |
| HCT-CI                                         |                 |                 |                 |
| 0                                              | 4 (21)          | 2 (15)          | 6 (19)          |

Unless otherwise indicated, data are n (%).

ATG, anti-thymocyte globulin; BM, bone marrow; CNI, calcineurin inhibitor; CR, complete response; Cy, cyclophosphamide; Flu, fludarabine; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; mMRD, mismatch related donor; MRD, matched related donor; MTX, methotrexate; MUD, matched unrelated donor; NMA, nonmyeloablative conditioning; PBSC, peripheral blood stem cell; PD, progressive disease; PR, partial response; PtCy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning; SD, stable disease; UCT, umbilical cord transplant.

*Response assessment using the Lugano classification and the International Workshop on Chronic Lymphocytic Leukemia criteria.

†CRS grading per modified Lee et al.

‡NT grading per National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE version 4.03).

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Graft-versus-host disease (GVHD) estimates were calculated using cumulative incidence, with relapse or death as competing risks. A Cox proportional-hazards model was used to study associations between clinical factors and overall mortality and nonrelapse mortality (NRM). We considered the following variables for univariate analysis: prior cytokine-release syndrome (CRS) or neurotoxicity (NT), time between CAR-T infusion and allo-HCT, hematopoietic cell transplantation comorbidity index (HCT-CI), conditioning regimen intensity, and disease-directed therapy between CAR-T therapy and allo-HCT. The study was approved by the institutional review board of Fred Hutch and was conducted in accordance with the Declaration of Helsinki.

Results

Between 2014 and 2017, 32 patients (ALL, n = 19; NHL, n = 8; CLL, n = 5) underwent allo-HCT after ≥1 CAR-T infusion. The median age at transplant was 46 years (range, 23-74). Three ALL patients (16%) had a previous allo-HCT, and 5 NHL patients (38%) had undergone autologous transplant before CAR-T therapy. Twenty-six patients (81%) had cyclophosphamide and fludarabine; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; mMRD, mismatch related donor; MRD, matched related donor; MMF, matched unrelated donor; NMA, nonmyeloablative conditioning; PBSC, peripheral blood stem cell; PD, progressive disease; PR, partial response; PTCy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning; SD, stable disease; UCT, umbilical cord transplant.

Table 1. (continued)

|                  | ALL (n = 19) | NHL/CLL (n = 13) | Entire cohort (N = 32) |
|------------------|-------------|-----------------|----------------------|
| 1                | 2 (11)      | 5 (39)          | 7 (22)               |
| 2                | 5 (26)      | 3 (23)          | 8 (25)               |
| 3                | 3 (15)      | 0 (0)           | 3 (9.5)              |
| 4                | 2 (11)      | 1 (8)           | 3 (9.5)              |
| 5                | 2 (11)      | 2 (15)          | 4 (12)               |
| 6                | 1 (5)       | 0 (0)           | 1 (3)                |
| **Donor type**   |             |                 |                      |
| MRD              | 3 (16)      | 2 (15)          | 5 (16)               |
| MUD              | 9 (50)      | 8 (62)          | 17 (53)              |
| mMURD            | 1 (4)       | 1 (8)           | 2 (6)                |
| Haploidentical   | 2 (4)       | 2 (15)          | 3 (9)                |
| UCT              | 5 (26)      | 0 (0)           | 5 (16)               |
| **Cell type**    |             |                 |                      |
| PBSC             | 13 (69)     | 13 (100)        | 26 (81)              |
| BM               | 1 (5)       | 0 (0)           | 1 (3)                |
| Cord             | 5 (26)      | 0 (0)           | 5 (16)               |
| **Conditioning regimen** |   |                 |                      |
| MAC              | 14 (74)     | 5 (39)          | 19 (59)              |
| RIC              | 2 (10)      | 3 (23)          | 5 (16)               |
| NMA              | 3 (16)      | 5 (38)          | 8 (25)               |
| **GVHD prophylaxis** |   |                 |                      |
| CNI + MMF        | 5 (26)      | 6 (48)          | 11 (35)              |
| CNI + MMF + sirolimus | 1 (5) | 2 (15) | 3 (9) |
| CNI + MTX        | 9 (48)      | 3 (23)          | 12 (38)              |
| CNI + MTX + abatacept | 3 (16) | 0 (0) | 3 (9) |
| CNI + MMF + PTCy | 1 (5)       | 1 (8)           | 2 (6)                |
| NCI + ATG        | 0 (0)       | 1 (8)           | 1 (3)                |

Unless otherwise indicated, data are n (%).

ATG, anti-thymocyte globulin; BM, bone marrow; CNI, calcineurin inhibitor; CR, complete response; Cy, cyclophosphamide; Flu, fludarabine; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; mMRD, mismatch related donor; MRD, matched related donor; MTX, methotrexate; MUD, matched unrelated donor; NMA, nonmyeloablative conditioning; PBSC, peripheral blood stem cell; PD, progressive disease; PR, partial response; PTCy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning; SD, stable disease; UCT, umbilical cord transplant.

*Response assessment using the Lugano classification17 and the International Workshop on Chronic Lymphocytic Leukemia18 criteria.
†CRS grading per modified Lee et al.19
‡NT grading per National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE version 4.03).20

In ALL patients, the median time from CAR-T therapy to allo-HCT was 72 days (range, 28-138). Two patients (10%) received therapy between CAR-T therapy and allo-HCT. Before allo-HCT, all ALL patients had a morphologic complete response (CR), and 18 (95%) were minimal residual disease negative by flow cytometry (sensitivity, 1:10 000). Eight of 10 ALL patients (80%) with an identified index clone by immunoglobulin heavy (IGH) chain sequencing had no malignant clone in marrow before allo-HCT. In NHL/CLL patients,
the median time to allo-HCT was 112 days (range, 55-456). Nine patients (69%) received interim therapy. At the time of allo-HCT, all patients (n = 13) had evidence of disease, and 6 patients (46%) had bulky lymphadenopathy ($\geq 5$ cm).

Nineteen patients (59%; 74% of ALL and 38% of NHL/CLL) received myeloablative conditioning (MAC). Stem cell graft sources included HLA-matched unrelated peripheral blood stem cells (PBSCs; 53%), HLA-matched related PBSCs (16%), umbilical cord blood (UCB; 16%, all ALL), haploidentical PBSCs (9%), and HLA-mismatched unrelated PBSCs (6%). The median HCT-CI was 2; 19 patients (59%) had HCT-CI $\geq 2$. Relevant transplant characteristics are summarized in Table 1.

The median follow-up after allo-HCT was 35 months. All patients achieved neutrophil engraftment (>1000 per cubic millimeter). The

### Table 2. Posttransplant complications in patients with prior CD19-targeted CAR-T treatment

| Acute GVHD | ALL (n = 19) | NHL/CLL (n = 13) | Entire cohort (N = 32) |
|------------|-------------|-----------------|----------------------|
| Grade 1    | 2 (10.5)    | 1 (7.7)         | 3 (9.4)              |
| Grade 2    | 8 (42.1)    | 6 (46.2)        | 14 (43.8)            |
| Grade 3    | 3 (15.8)    | 2 (15.4)        | 5 (15.6)             |
| Grade 4    | 1 (5.3)     | 2 (15.4)        | 3 (9.4)              |
| 1-y cumulative incidence of grade 2-4 (95% CI), % | 63 (40-86) | 77 (51-100) | 69 (52-85) |
| 1-y cumulative incidence of grade 3-4 (95% CI), % | 21 (2-40)  | 31 (4-57)      | 25 (10-40) |

**Chronic GVHD**

| No | Yes |
|----|-----|
| 15 (78.9) | 4 (21.1) |
| 12 (92.3) | 1 (7.7) |
| 27 (84.4) | 5 (15.6) |

**Viral and fungal infections**

| Parainfluenza | HSV-1 stomatitis | Adenovirus hepatitis | CMV gastroenteritis | RSV | Aspergillosis | Other fungal | Toxoplasmosis |
|---------------|------------------|----------------------|--------------------|-----|--------------|--------------|--------------|
| 2 (10.5)      | 1 (5.3)          | 1 (5.3)              | 1 (5.3)            | 1 (5.3) | 1 (5.3)     | 1 (5.3)     |
| 0 (0.0)       | 0 (0.0)          | 0 (0.0)              | 2 (15.4)           | 0 (0.0) | 0 (0.0)     | 0 (0.0)     |
| 2 (6.2)       | 1 (3.1)          | 3 (3.1)              | 3 (9.4)            | 3 (9.4) | 3 (9.4)     | 3 (9.4)     |

**Nonhematologic toxicities**

| Neurologic: PRESS | Cardiac: atrial fibrillation | Hepatic: cholecystitis | Renal: TMS | Renal: other renal | GI: bleeding | Pulmonary: DAH | Pulmonary: PE |
|------------------|-----------------------------|------------------------|------------|-------------------|-------------|----------------|--------------|
| 1 (8)            | 1 (5)                       | 1 (5)                  | 0 (0)      | 0 (0)             | 0 (0)       | 2 (10.5)       | 0 (0)        |
| 0 (0)            | 1 (8)                       | 0 (0)                  | 3 (23)     | 0 (0)             | 1 (8)       | 1 (8)          | 1 (8)        |
| 1 (3)            | 2 (6)                       | 1 (3)                  | 3 (9)      | 2 (6)             | 1 (3)       | 3 (9)          | 1 (3)        |

**Cause of death**

| Disease progression | GVHD | Fungal infection | Sepsis | Pulmonary | PE | IPS | Total |
|---------------------|------|-----------------|--------|-----------|----|-----|-------|
| 2 (10.5)            | 1 (5.3) | 1 (5.3) | 1 (5.3) | 0         | 0  | 1   | 6     |
| 2 (15.4)            | 2 (15.4) | 1 (7.7) | 0       | 1 (7.7)   | 1 (7.7) | 1 (3.1) | 6 (31) |
| 4 (12.5)            | 3 (9.4) | 2 (6.2) | 1 (3.1) | 1 (3.1)   | 1 (3.1) | 12 (37.5) |

Unless otherwise indicated, data are n (%).

CMV, cytomegalovirus; DAH, diffuse alveolar hemorrhage; GI, gastrointestinal; HSV, herpes simplex virus; IPS, idiopathic pulmonary syndrome; PE, pulmonary embolus; PRESS, posterior reversible encephalopathy syndrome; RSV, respiratory syncytial virus.
median times to an absolute neutrophil count $\geq 500$ and $\geq 1000$ per cubic millimeter were 16 and 18.5 days, respectively. With the exception of 3 patients with a higher platelet goal (50 000-100 000) because of increased hemorrhagic risk, all patients achieved platelet engraftment ($>70 000$ per cubic millimeter without transfusion) by day 100 after hematopoietic cell transplantation. Median time to achieve a platelet count $\geq 20 000$ and $\geq 70 000$ per cubic millimeter were 12 and 14 days, respectively. All patients received platelet transfusions (median, 6.5 episodes) and red cell transfusions (median, 5.5 episodes) in the first 100 days. All patients achieved 100% donor CD3 and CD33 chimerism in blood at day 28. CAR-Ts were detected at the limit of detection by quantitative polymerase chain reaction in only 3 patients (1 after MAC) after achieving 100% donor CD3 and CD33 chimerism in blood at day 28. CAR-Ts were detected at the limit of detection by quantitative polymerase chain reaction in only 3 patients (1 after MAC) after day 28.

One-year estimates of grade 2-4 and grade 3-4 acute GVHD were 69% (95% confidence [CI], 52-85) and 25% (95% CI, 10-40), respectively. The median time to acute GVHD was 27 days. Five (16%) patients developed chronic GVHD a median of 305 days after allo-HCT, 24 patients (75%) at allo-HCT but because of increased hemorrhagic risk, all patients achieved platelet transfusions (median, 5.5 episodes) in the first 100 days. All patients achieved 100% donor CD3 and CD33 chimerism in blood at day 28. CAR-Ts were detected at the limit of detection by quantitative polymerase chain reaction in only 3 patients (1 after MAC) after allo-HCT.

Viral and fungal infections are summarized in Table 2. Eleven patients (34%) had bacterial infections: coagulase-negative Staphylococcus (n = 3), Enterococcus spp. (n = 3), Escherichia coli (n = 2), Streptococcus mitis (n = 2), Clostridium difficile (n = 2), and Legionella pneumophila (n = 1). Six patients (18%) had invasive fungal infections, including 3 with documented aspergillosis. One patient had vitreous toxoplasmosis. Six ALL patients died from disease progression (n = 2), Aspergillus pneumonia (n = 1), bacterial sepsis (n = 1), GVHD (n = 1), and idiopathic pulmonary syndrome (n = 1). Six NHL/CLL patients died because of disease progression (n = 2), GVHD (n = 2), pulmonary emboli (n = 1), and fungal infection (n = 1) (Table 2). At a median follow-up of 36 months for ALL patients, 1-year estimate of overall survival (OS) was 58% (95% CI, 40-85), and the 100-day and 1-year NRM estimate rates were 16% and 21%, respectively. For NHL/CLL patients, at a median follow-up of 35 months, 1-year estimate of OS was 59% (95% CI, 37-95), and the 100-day and 1-year NRM rates were 15% and 33%, respectively (Figure 1).

In ALL patients, longer time from CAR-T therapy to allo-HCT ($\geq 80$ days) was associated with higher risk for death (hazard ratio [HR], 4.01; 95% CI, 1.14-14.0; $P = .03$) and higher NRM (HR, 4.4; 95% CI, 0.54-21.1; $P = .19$). On the other hand, in NHL/CLL patients, there was a trend toward lower NRM (HR, 0.14; 95% CI, 0.01-1.72; $P = .12$) and a lower risk for fungal or systemic viral infection (odds ratio, 0.04; 95% CI, 0.001-0.64; $P = .04$) when allo-HCT was done later ($\geq 80$ vs $< 80$ days) after CAR-T therapy. Using a MAC regimen (vs reduced-intensity conditioning or nonmyeloablative conditioning) was associated with a higher risk for death (HR, 3.83; 95% CI, 0.91-16.6; $P = .06$) and NRM (HR, 8.3; 95% CI, 0.90-100; $P = .06$) in NHL/CLL patients. Higher HCT-CI was associated with a trend toward higher overall mortality (HR, 1.37; 95% CI, 0.9-2.01; $P = .11$) and NRM (HR, 1.43; 95% CI, 0.9-2.28; $P = .12$).

**Discussion**

Treatments, such as allo-HCT, may improve the durability of remissions achieved after CAR-T therapy, or they can be used after progression post–CAR-T treatment. Prior CAR-T therapy can potentially increase the posttransplant toxicity by inducing immunosuppression and endothelial damage. In this study, we focused on post–allo-HCT...
complications in patients with prior CAR-T treatment. The study demonstrated the feasibility of this approach and did not reveal a signal indicating an increased risk for specific adverse events after allo-HCT.

At our institution (Fred Hutch/University of Washington), allo-HCT is commonly offered as consolidative therapy to ALL patients who achieve a remission after CAR-T therapy. On the other hand, NHL/CLL patients are usually referred for allo-HCT only with refractory or relapsed disease after CAR-T therapy (Figure 2).

Given this differential approach in utilizing allo-HCT, which could potentially induce a bias in the interpretation of data when analyzed in combination, we reported the data separately for the 2 cohorts (ALL vs NHL/CLL). The main purpose of the study was to detect any possible adverse event that was disproportionately more common in this setting compared with the known post–allo-HCT benchmark.

Although such risk was not observed in this study, these patients should be monitored closely for potential toxicities that may become evident as more patients are treated with allo-HCT after CAR-T therapy.

One notable finding in the ALL cohort was the improved outcomes in patients who received allo-HCT earlier rather than later after CAR-T therapy. These data support our current practice of early transplant discussions and HLA typing for suitable ALL patients undergoing CAR-T therapy. The benefit of performing an earlier allo-HCT was not seen in the NHL/CLL cohort. To explain this difference, it should be noted that fewer patients in the ALL group received interim therapy compared with NHL/CLL patients, who more commonly required additional treatment of disease control before allo-HCT (10.5% vs 69%). This may explain, at least in part, the higher toxicity of allo-HCT when it was done earlier in NHL/CLL patients.

In summary, the incidences of adverse events after allo-HCT were not above those expected in these high-risk patients and the incidence and kinetics of hematopoietic recovery, and the incidences of infections and GVHD were comparable to previous studies conducted in the absence of prior CAR-T therapy.11-16 This study represents a heterogenous group of patients with a variety of treatments and transplant details. This was inevitable given the relatively limited experience with CAR-T therapy and the even smaller number of patients with subsequent allo-HCT. Nevertheless, and although the results should be interpreted with caution, the data provide a platform for the design of prospective studies to address the efficacy, cost effectiveness, and timing of allo-HCT after CAR-T immunotherapy.
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Authorship

Contribution: M.S., J.G., K.A.H., J.M.V., D.G.M., and C.J.T. designed the research; M.S., J.G., K.A.H., J.M.V., F.M., K.A.H., A.L., A.V.H., M.L.S., S.C., X.C., R.D.C., B.G.T., A.K.G., B.M.S., D.G.M., and C.J.T. provided and analyzed data; M.S. and C.J.T. wrote the manuscript; and all authors reviewed, edited, and approved the final manuscript.

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References

1. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439-448.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
3. Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.
4. 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(6):2123-2138.
5. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin’s lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016;8(355):355ra116.
6. Turtle CJ, Hay KA, Hanafi LA, et al. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol. 2017;35(26):3010-3020.
7. Chow VA, Gopal AK, Maloney DG, et al. Outcomes of patients with large B-cell lymphomas and progressive disease following CD19-specific CAR T-cell therapy [abstract]. Blood. 2018;132(suppl 1). Abstract 94.
8. Hay KA, Gauthier J, Hirayama AV, et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood. 2019;133(15):1652-1663.
9. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 2017;7(12):1404-1419.
10. 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(4):625-638.
11. Fenske TS, Ahn KW, Graff TM, et al. Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. Br J Haematol. 2016;174(2):235-248.
12. Shah NN, Ahn KW, Litovitch C, et al. Outcomes of Medicare-age eligible NHL patients receiving RIC allogeneic transplantation: a CIBMTR analysis. Blood Adv. 2018;2(8):933-940.
13. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. Infect Dis Clin North Am. 2010;24(2):257-272.

14. Segal E, Martens M, Wang HL, et al. Comparing outcomes of matched related donor and matched unrelated donor hematopoietic cell transplants in adults with B-cell acute lymphoblastic leukemia. Cancer. 2017;123(17):3346-3355.

15. Rosko A, Wang HL, de Lima M, et al. Reduced intensity conditioned allograft yields favorable survival for older adults with B-cell acute lymphoblastic leukemia. Am J Hematol. 2017;92(1):42-49.

16. Cassaday RD, Storer BE, Sorror ML, et al. Long-term outcomes of patients with persistent indolent B cell malignancies undergoing nonmyeloablative allogeneic transplantation. Biol Blood Marrow Transplant. 2015;21(2):281-287.

17. Cheson BD, Fisher RI, Barrington SF, et al; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.

18. Hallek M, Cheson BD, Catovsky D, et al; International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456.

19. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome [published correction appears in Blood. 2016;128(11):1533]. Blood. 2014;124(2):188-195.

20. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 9 October 2019.