Safety and efficacy of allogeneic hematopoietic stem cell transplantation in R/R B-NHL patients with disease progression after CAR-T therapy

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Research Article

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Abstract

Background: R/R B-NHL patients with disease progression after CAR-T therapy have poor prognosis and no standard chemotherapy regimen has been defined. We aimed to explore whether receiving allo-HSCT could improve the outcomes of R/R B-NHL patients who have disease progression after CAR-T therapy.

Methods: From October 2017 to June 2021, we retrospectively report outcomes of R/R B-NHL patients with disease progression after CAR-T cell treatment, then receiving allo-HSCT.

Results: Among 9 patients, 4 were males and 5 females, with a median age of 44 (27-52) years. 5 patients were diagnosed refractory/relapsed diffuse large B cell lymphoma, 1 patient was Burkitt lymphoma, 1 was B lymphoblastic lymphoma, 1 was transformed DLBCL and 1 was gray zone lymphoma. 8/9 donors were haploidentical family member, 1/9 donor was identical sibling. The median time from CAR-T treatment to transplantation was 2.3 (1.0-12.3) months. 9/9 patients obtained complete engraftment. The median time of neutrophil implantation was 12 (11- 19) days, and 13 (9-20) days of platelet implantation. The median follow-up was 7.9 (3.4-48.6) months. 4/9 patients received CR and 1/9 patient received PR during the follow up. The objective response rate (ORR) was 55.6%. The six-months overall survivaln (OS) and progression-free survival (PFS) were 66.7% and 33.3%, respectively. 1 case experienced acute graft-versus-host disease□aGVHD□grade □, 1 case with aGVHD grade □. Among 5 survivals, localized chronic GVHD occurred in 1 patient. During the follow up, four patients have died and the causes were disease relapses and progressions (2 patients), acute renal failure (1 patient), severe pulmonary infection (1 patient). No-relapse mortality was 22.2%.

Conclusion: The present study demonstrated that allo- HSCT is a feasible and safe choice with favorable outcome for R/R B-NHL patients with disease progression after CAR-T therapy.

Background

B cell Non-Hodgkin's Lymphoma (B-NHL) is a group of histologically and biologically distinct malignancies that originate from B-cells. With the emergence of rituximab and combined chemotherapies in B-NHL, the response and survival rates have improved dramatically. However, approximately 10–15% of patients present with primary refractory disease and 30–40% relapse after first-line treatment.[1–3] The prognosis of patients with refractory disease is poor: A multicohort, retrospective non-Hodgkin's lymphoma research study (SCHOLAR-1) showed that the objective response rates (ORRs) and complete response (CR) rates for patients with R/R B-NHL were only 26% and 7%, respectively, with a median overall survival (OS) of 6.3 months.[3]

For patients with R/R B-NHL, chimeric antigen receptor T cell targeting CD19 (CAR-T19) is a new immunotherapeutic strategy. CAR T cells are genetically engineered to allow T cells to recognize and interact with tumor cells, leading to target cell lysis and the subsequent effective and profound clearance of tumor cells.[4] High response rates were observed in adult patients with R/R B-NHL receiving CAR-T19 with ORRs ranging from 50–82%.[5–8] Despite this impressive efficacy, the benefits are often transient, and relapse occurs in 30–50% patients who receive CD19 CAR T cells infusion.

R/R B-NHL patients with disease progression after CAR-T therapy still have poor prognosis and no standard chemotherapy regimen has been defined. Therefore, it is apparent that novel treatment modalities are urgently

needed for them. For such patients, allogeneic hematopoietic stem cell transplantation (allo-HSCT) should be considered as a treatment option. An expert panel opinion from the American Society for Transplantation and Cellular Therapy suggests that allo-HSCT may be considered for patients with CR post CAR T-cell therapy after individualized evaluation, whereas in patients with relapse/progression allo-HSCT should be included among treatment options.[9] However, existing data regarding the role of allo-HSCT after CAR T-cell therapy is rather limited and no long-term outcomes are available.

This retrospective analysis aimed to explore whether receiving allo-HSCT could improve the outcomes of R/R B-NHL patients who have disease progression after CAR-T therapy.

Patients And Methods

We performed a retrospective analysis of patients with R/R B-NHL who relapsed after CAR-T therapy at the First Affiliated Hospital of Soochow University. From October 2017 to June 2021, we report outcomes of R/R B-NHL patients with disease progression after CAR-T cell treatment, then receiving allo-HSCT. In our analysis, 11 patients' clinical data were collected and a total of 2 patients were not eligible for the analysis due to the lack of efficiency evalulation of allo-HSCT. All patients were diagnosed based on histopathologic examinations and the clinical stages were defined according to the Ann Arbor clinical staging. The overall survival (OS), progression-free survival (PFS) and no-relapse mortality were analyzed. OS was defined as the time from diagnosis to death from any cause. PFS was defined as the time from diagnosis to relapse or progressive disease or death from any cause, whichever came first.

Results

Patient characteristics

Among 9 patients, 4 were males and 5 females, with a median age of 44 (27–52) years. 5 patients were diagnosed refractory/relapsed diffuse large B cell lymphoma, 1 patient was Burkitt lymphoma, 1 was B lymphoblastic lymphoma, 1 was transformed DLBCL and 1 was gray zone lymphoma. Seven patients (77.8%) had B symptoms, three had bone marrow involvement at the time of diagnosis (33.3%). 7/9 patients were at stage Ⅲ and 2/9 were at stage Ⅳ. IPI ranged from 2 to 4. IPI was 2 or 3 in four patients, and 4 in one patient. All patients had received CAR-T therapy before allo-HSCT. Four patients received CD19 directed CAR-T treatment, four patients received CD19/22 CAR-T and one received CD19/30 CAR-T. With median follow-up 7.9 months, all patients had PD after CART. Demographic and clinical variables of patients with PD are detailed in Table 1.

Table 1
Clinical features of patients (n = 9)

	Patient	
	No %	
Sex		
Male	4	44.4%
Female	5	55.6%
Age (years)		
Range	27–52	
Median	44	
ECOG performance stage		
0–1	6	66.7%
≥ 2	3	33.3%
Ann Arbor clinical stage		
□	2	22.2%
□	7	77.8%
LDH higher than ULN	6	66.7%
Disease type		
DLBCL	5	55.6%
Transformed DLBCL	1	11.1%
Gray zone lymphoma	1	11.1%
Burkitt lymphoma	1	11.1%
B lymphoblastic lymphoma	1	11.1%
Prior therapies		
Range	3–10	
Median	9	
IPI	0	0
0–1		
2	4	44.4%
3	4	44.4%
4	1	11.1%

Allo-HSCT characteristics and hematopoietic reconstruction

The median time from CAR-T treatment to transplantation was 2.3 (1.0-12.3) months. 8/9 donors were haploidentical family member, 1/9 donor was identical sibling. The conditioning regimens included BU/CY (busulfan, cyclophosphamide) and TBI/CY treatments. 9/9 patients obtained complete engraftment. The median time of neutrophil implantation was 12 (11–19) days, and 13 (9–20) days of platelet implantation. The median monocyte(MNC) was 8.25 (2.16 to 15.02) $\times 10^8$/kg and CD34 + cells ranged from 0.95×106 to 7.36$\times 10^6$cells/kg (median 2.64$\times 10^6$ cells/kg). (Table 2).

Table 2
Treatment characteristics and response(n = 9)

Patient	Time (d)	Type of donors	Type of transplantation	Conditioning regimens	MNC (×108 /kg)	GVHD	Efficiency	CD34 + cell
1	51	MMRD	PBSCT	TBI/Cy	15.02	CsA + MMF + MTX	CR	7.36
2	370	MMRD	BMT + PBSCT	DAC + Bu/Cy	3.23	CsA + MMF + MTX	PD	0.95
3	246	MMRD	BMT	DCA + Bu/Cy + ATG	8.25	CsA + MMF + MTX	CR	3.87
4	45	MMRD	BMT + PBSCT	Bu/Cy	2.16	CsA + MMF + MTX	CR	2.22
5	101	MMRD	BMT + PBSCT	Bu/Cy	5.28	CsA + MMF + MTX	PD	2.64
6	31	MMRD	BMT + PBSCT	TBI/Cy	4.45	CsA + MMF + MTX	CR	1.96
7	50	MMRD	BMT + PBSCT	Bu/Cy	10.33	CsA + MMF + MTX	PD	5.49
8	133	MSD	PBSCT	DAC + Bu/Cy	14.19	CsA + MTX	PR	3.68
9	68	MMRD	BMT + PBSCT	Bu/Cy	10.6	CsA + MMF + MTX	PD	1.56

Time: The time from CAR-T treatment to transplantation, CR complete remission, PR partial remission, PD progression disease

Efficiency

The median follow-up was 7.9 (3.4–48.6) months. 4/9 patients received CR and 1/9 patient received PR during the follow up. The objective response rate (ORR) was 55.6%. The six-months overall survivaln (OS) and progression-free survival (PFS) were 66.7% and 33.3%, respectively.

Safety

1 case experienced acute graft-versus-host disease(aGVHD)grade Ⅱ, 1 case with aGVHD grade Ⅲ. Among 5 survivals, localized chronic GVHD occurred in 1 patient. During the follow up, four patients have died and the

causes were disease relapses and progressions (2 patients), acute renal failure (1 patient), severe pulmonary infection (1 patient). No-relapse mortality rate was 22.2%.

Discussion

CAR-T therapy is a promising new treatment option for patients with multiply relapsed and refractory (R/R) B cell non-Hodgkin's lymphoma. Patients with chemorefractory DLBCL treated with conventional therapies have a CR rate of 7%, a median OS of 6 months, and 1-year OS rate of 28%, as illustrated by the retrospective SCHOLAR-1 study.[4] The three CAR-T pivotal trials recruited heavily pre-treated patients, the majority of whom were chemorefractory (76% in ZUMA-1, 55% in JULIET, and 67% in TRANSCEND). The overall response rates (ORR) ranged from 52–74% with 1-year OS rates of 48–59%,[8, 10] demonstrating that CAR-T cell therapies have altered the natural history of chemorefractory DLBCL, in comparison with nonrandomized historical controls.[11] Although CAR T-cell therapy is accompanied by unprecedented rates of initial response, emerging data reveal the existence of resistance mechanisms to CAR T-cell therapy. In DLBCL, approximately 60% of patients are expected to progress or relapse after CAR T-cell therapy, with most events occurring within the first 3–6 months, [12] thus representing a new unmet need in the treatment of this disease.

Currently there is no standard of care treatment options for LBCL patients post CAR-T failure. Data from the US CART Consortium included 136 CAR-T failures that received checkpoint inhibitor based, lenalidomide based, chemotherapy, and radiation with an ORR of 40%, 19%, 18%, and 30%, respectively. The overall median PFS with each treatment category was very short (48–88 days).[13] Thus, there is interest in understanding the role of newly approved agents/regimens for LBCL. FDA-approved therapies for R/R LBCL which can be employed after CAR-T failure include pola-BR, tafa-len, and selinexor, which are not available in China.[14] Thus, to those who achieve a type of response post CAR-T failure, a consolidation with allo-HSCT may be considered. However, existing data regarding the role of allo-HSCT after CAR T-cell therapy is rather limited and no long-term outcomes are available. In the ZUMA-1 trial, 2 patients who had a response underwent allo-HSCT, while in the JULIET trial no patient proceeded to transplantation while having a response. However, 6 patients who were unresponsive to CAR T-cells proceeded ultimately to allo-HSCT.[8, 15] In a smaller study of 51 B-NHL patients with progressive disease after anti-CD19 CAR-T therapy, 4 patients (8%) eventually received an allo-HSCT with 2 of them remaining alive after 12 months of disease progression. Given the inadequate data, there are no guidelines regarding the role of allo-HSCT in B-NHL after receiving CAR T-cells.[16]

In this study, we analyzed the data of nine R/R B-NHL patients who had received allo-HSCT after CAR-T failure retrospectively. CRS occurred in 9/9 patients (100%) during CAR-T therapy, including 7/9 (77.8%) patients assessed as grade 1 or 2 and 2/9 (22.2%) as grade 3. All patients had received allo-HSCT post CAR-T failure. The median time from CAR-T treatment to transplantation was 2.3 (1.0-12.3) months. 9/9 patients obtained complete engraftment. 4/9 patients received CR and 1/9 patient received PR during the follow up. The ORR was 55.6%. The six-months OS and PFS were 66.7% and 33.3%, respectively. The adverse events associated with pretreatment are mainly gastrointestinal reactions such as vomiting and mild diarrhea. There were no graft failures, and no episodes of grade 4 acute graftversus-host disease (GVHD); only 2/9 (22.2%) of patients had grade 2 to 3 GVHD, and 1/9 (11.1%) had localized chronic GVHD. The non-relapse mortality rate was 22.2%.

In summary, the case data of this group show that allo-HSCT in R/R B-NHL patients with disease progression after CAR-T therapy has a good efficacy. Pretreatment tolerable, related adverse events, transplant-related risks and post-transplant related complications are acceptable. For patients who have available donors, allo-HSCT should be considered as a treatment option. Long term follow-up and randomized studies are needed to further evaluate the efficacy and safety of allo-HSCT in R/R B-NHL patients who have CAR-T failure.

Conclusion

The present study demonstrated that allo-HSCT is a feasible and safe choice with favorable outcome for R/R B-NHL patients with disease progression after CAR-T therapy.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics committee of the First Afliated Hospital of Soochow University. We have obtained written and signed consent to publish this paper from these patients.

Consent for publication: All authors have consented for publication.

Availability of data and materials: The datasets during and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: HH designed the research; MC participated in the design of the study and performed the research; SA analyzed the data. YZ and MJ performed the statistical analysis. LY and LK helped to analyze the data. ZJ interpreted the data. CL critically assessed the manuscript; DW and HH revised the manuscript and approved the final version, and all authors read and approved the final manuscript.

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Figures

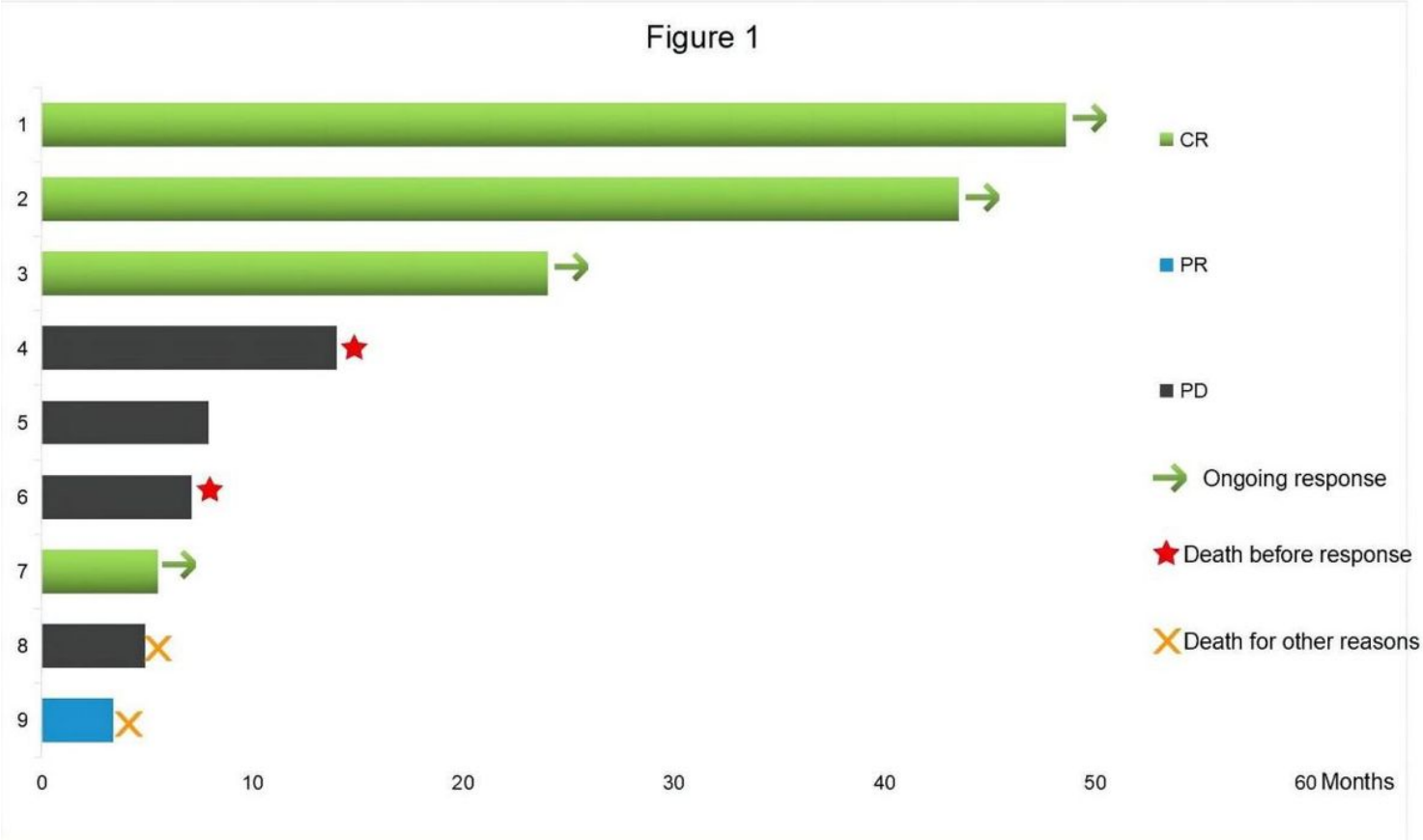

Figure 1

Legend not included with this version