Cytopenia after CAR-T cell therapy: Analysis of 63 patients with relapsed and refractory B-cell non-Hodgkin lymphoma

TINGTING QIU, LUAN HU, YONGTIAN ZHANG, YING WANG, SHA MA, DEPENG LI, ZHENYU LI and KAILIN XU

Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221002, P.R. China

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Abstract. The present study aimed to determine the clinical characteristics of cytopenia in patients with relapsed and refractory B-cell non-Hodgkin lymphoma (B-NHL) who were treated with chimeric antigen receptor T-cell (CAR-T) therapy. Thus, a total of 63 patients with relapsed and refractory B-NHL who underwent CAR-T therapy between March 2017 and October 2021 were retrospectively selected for analysis. Neutropenia, anemia and thrombocytopenia at grade ≥3 occurred in 48 (76.19%), 16 (25.39%) and 15 (23.80%) cases, respectively. The results of a multivariate analysis demonstrated that the baseline absolute neutrophil count (ANC) and hemoglobin concentration were independent risk factors for grade ≥3 cytopenia. A total of 3 patients died early and were therefore excluded from the present study. Furthermore, cell recovery was examined at day +28 after infusion; 21 patients (35%) did not recover from cytopenia and 39 patients (65%) recovered. A multivariate analysis demonstrated that the baseline ANC <2.29x10^9/l, baseline hemoglobin <114.50 g/l and baseline IL-6 >21.43 pg/l were independent risk factors affecting hemocyte recovery. In conclusion, patients with relapsed and refractory B-NHL exhibited an increased incidence of grade ≥3 hematologic toxicity following CAR-T cell therapy, while baseline blood cell and IL-6 levels are independent risk factors for hemocyte recovery.

Introduction

Chimeric antigen receptor T-cells (CAR-T) recognize tumor antigen-specific receptors through gene recombination (1). CAR-T therapy produced encouraging results in relapsed and refractory hematological malignancies, including B-cell acute lymphoblastic leukemia (B-ALL) (2,3), non-Hodgkin lymphoma (NHL) (4,5) and multiple myeloma (MM) (6,7). Although clinical trials of CAR-T therapy have demonstrated marked efficacy, patients may experience associated adverse events, including cytokine release syndrome (CRS), neurological toxicity (NT) and macrophage activation syndrome. Of note, cytopenia is common in patients following CAR-T therapy and numerous patients experience cytopenia prior to CAR-T cell infusion. Furthermore, blood cells are further reduced following CAR-T therapy and patients are prone to infection, bleeding and other complications that may be life-threatening. At present, large-scale reports of cytopenia in patients with B-cell NHL (B-NHL) who underwent CAR-T therapy are lacking. Thus, the present study aimed to determine potential changes in cytopenia in patients with relapsed and refractory B-NHL following CAR-T therapy and provide a theoretical basis for early intervention in patients with CAR-T-associated complications.

Materials and methods

Patients. A retrospective analysis was performed using patients with relapsed and refractory B-NHL. All patients had been admitted to the Hematology Department of The Affiliated Hospital of Xuzhou Medical University (Xuzhou, China) between March 2017 and October 2021 and had complete clinical data. All patients were enrolled in the CAR-T cell clinical trials (NCT02782351, NCT02794961, NCT02903810 and NCT03207178). Patients who met the following criteria were included in the present study: i) A confirmed diagnosis of relapsed and refractory B-NHL; ii) an expected survival of >12 weeks; iii) provided written informed consent. Patients were excluded for the following reasons: i) Other major systemic disease, such as severe respiratory failure, heart function grade III to IV or uremic phase; ii) complications with severe and uncontrollable present infection, severe coagulation dysfunction, disseminated intravascular coagulation or severe thrombosis; iii) active viral hepatitis B or C; iv) autoimmune diseases or other chronic diseases that depend on immunosuppressants or hormone therapy; v) psychological diseases that do not allow for coordination with treatment or efficacy evaluations; and vi) pregnancy or lactation. The present study was approved by the Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Xuzhou, China).

Correspondence to: Professor Kailin Xu, Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, 99 West Huaihai Road, Xuzhou, Jiangsu 221002, P.R. China
E-mail: lihmd@163.com

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Manufacture of CAR-T cells. Appropriate amounts of mononuclear cells (usually $1x10^9$) were sorted from the peripheral blood of patients and prepared by a third-party company *in vitro*. Genetic engineering technology was used to form second generation CAR-T cells expressing target antibody fragments and the transmembrane-activated signaling domain of the T-cell receptor, intracellular linking 4-1BB or CD28 co-stimulatory molecules were fused (8). Strict quality control and aseptic technique were performed during CAR-T cell culture.

CAR-T therapy and monitoring. CAR-T cell infusion was performed on Day 0 and each patient was administered fludarabine (35 mg/m^2 on day -5 to -3) and cyclophosphamide (750 mg/m^2 on day -5) as pre-treatment. Enrolled patients were transfused with a total of $1x10^6$/kg CAR-T cells and vital signs and patient condition were closely observed during infusion. Specific factors were monitored from enrollment to the end of follow-up after CAR-T cell therapy, including: i) Vital signs, such as body temperature, heart rate and blood pressure, examined 1-2 times per day prior to CAR-T cell infusion, following CAR-T cell infusion and at each follow-up after discharge; and ii) routine blood examination, including liver and kidney function, C-reactive protein (CRP), ferritin and IL-6. CRS, NT grading and efficacy evaluation were performed according to a previously published procedure (9). All factors were examined prior to pre-treatment and CAR-T cell infusion, and periodically following CAR-T cell infusion. Follow-up was completed in both inpatient and outpatient settings.

Cytopenia classification and hematologic recovery. Cytopenia was graded according to the Common Terminology Criteria for Adverse Events (version, 4.0) (10). Grade 3 or higher cytopenia was defined as absolute neutrophil count (ANC) $<1.0x10^9$/l, hemoglobin <80 g/l and platelet count $<50x10^9$/l. Hematologic recovery was defined as ANC $\geq1.0x10^9$/l, hemoglobin ≥80 g/l and platelet count $\geq50x10^9$/l for three consecutive days without granulocyte-stimulating factors or blood transfusions. According to the hematologic recovery observed on day +28, patients were divided into recovered and unrecovered groups. Of note, any series of blood cells that did not recover were classified as the unrecovered group.

Statistical analysis. Data were analyzed using SPSS (version, 26.0; IBM Corp.). The single-sample Wilcoxon signed-rank test was used to test whether a normal distribution was present. Continuous variables of non-normal distribution were described using the median (range) and the Mann-Whitney U-test was used for intergroup comparisons. Categorical variables were evaluated using the Chi-squared test or Fisher's exact test. A logistic regression model was used to analyze univariate and multivariate influencing factors. Receiver operating characteristic (ROC) curve analysis was used to obtain the optimal cut-off values. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. According to the inclusion and exclusion criteria, a total of 63 patients with relapsed and refractory B-NHL were enrolled in the present study, with a median age of 46 years (range, 21-72 years), including 45 males (71.42%) and 18 females (28.57%), with a male-to-female ratio of 2.5:1. Of note, 47 cases (74.60%) were primary type diffuse large B-cell lymphoma (DLBCL), including 4 cases of follicular cell lymphoma. The present study also included 4 cases (6.34%) of primary central DLBCL, 2 cases (3.17%) of primary mediastinal DLBCL, 5 cases (7.93%) of follicular cell lymphoma, 4 cases (6.34%) of B-cell lymphoma leukemia and 1 case (1.58%) of mantle cell lymphoma. In addition to 4 patients with B-cell lymphoma leukemia, 4 patients exhibited bone marrow involvement. The median number of prior chemotherapies was 8 (range, 3-26), and 4 patients (6.34%) received autologous hematopoietic stem cell transplantation (HSCT). Types of CAR-T infusion included 11 cases (17.46%) of CD19, 9 cases (14.28%) of CD20, 23 cases (36.50%) of CD19-CD20, 19 cases (30.15%) of CD19-CD22 and 1 case (1.58%) of CD20-NK. Bridging therapy was permitted for the patients before CAR-T treatment. Only nine patients received bridging therapy, mainly low-dose chemotherapy including CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), reduced ESHAP (etoposide, cisplatin, cytarabine and methylprednisolone), and one patient received lenalidomide and zanubrutinib. A total of 2 patients who were administered anti-CD19 and CD22 CAR cells received CD20 monoclonal antibody in addition. Following CAR-T cell infusion, 44 (69.84%) patients experienced CRS. Of these, 4 patients (6.34%) developed grade ≥3 CRS and 40 patients (63.49%) developed grade 1-2 CRS. In addition, 3 patients (4.76%) developed grade 3 NT and presented with recurrent seizures, and a total of 7 patients (11.11%) developed grade 1 NT and presented with headaches. Efficacy was evaluated 30 days following infusion and 3 patients who died early were excluded. Results of the present study demonstrated that the overall response rate was 65%, including 11 cases (18.3%) with complete response, 28 cases (46.7%) with partial response, 12 cases (20%) with stable disease and 9 cases (15%) with progressive disease (Table SI).

Occurrence of cytopenia. A total of 32 out of 63 patients (50.79%) with B-NHL experienced at least one series of baseline cytopenia prior to CAR-T therapy, including 18 patients (28.57%) with a median ANC of $3.15x10^9$/l ($0.61-11.35 x10^9$/l), 22 patients (34.92%) with a median hemoglobin concentration of 114 g/l (51-165 g/l) and 9 patients (14.28%) with a median platelet count of $178x10^9$/l ($43-447x10^9$/l). Following CAR-T therapy, 61 patients (96.82%) experienced neutropenia, 46 patients (73.01%) experienced anemia and 17 patients (26.98%) experienced thrombocytopenia. Of these, 48 patients (76.19%) experienced grade ≥3 neutropenia, 16 patients (25.39%) experienced grade ≥3 anemia and 15 patients (23.80%) experienced grade ≥3 thrombocytopenia. The median lowest values of ANC, hemoglobin concentration and platelet count were $0.64x10^9$/l ($0.02-2.31x10^9$/l), 100 g/l (32-137 g/l) and $121x10^9$/l ($2-307x10^9$/l), respectively. Patients achieved the lowest ANC at a median time of day 5 (range, 0-27 days), the lowest hemoglobin at a median time of day 8 (range, -5-28 days) and the lowest platelet count at a median time of day 10 (range, 0-28 days) (data not shown).

Factors associated with grade ≥3 cytopenia. To determine the risk factors associated with grade ≥3 cytopenia following

Table I. Analysis of risk factors for cytopenia above grade 3.

Characteristic [normal ranges]	Cytopenia group	No cytopenia group	Univariate analysis P	Multivariate analysis	
				OR (95% CI)	P-value
Gender			0.195		
Male	32 (66.66)	13 (86.67)			
Female	16 (33.34)	2 (13.33)			
Age, years	47 (21-72)	45 (24-70)	0.600		
ECOG score	2 (0-3)	1 (0-3)	0.026	1.935 (0.761-4.919)	0.166
Number of prior chemotherapies, times	8 (3-24)	10 (6-26)	0.147		
Prior autologous HSCT			1.000		
Yes	3 (6.25)	1 (6.67)			
No	45 (93.75)	14 (93.33)			
Bone marrow involvement			0.667		
Yes	7 (14.5)	1 (6)			
No	41 (85.5)	14 (94)			
Targets of CAR-T cell			0.503		
CD19	8 (16.67)	3 (20)			
CD20	7 (14.58)	2 (13.33)			
CD19-CD20	17 (35.41)	6 (40)			
CD19-CD22	16 (33.33)	3 (20)			
CD19-NK	0 (0)	1 (6.67)			
CRS			0.380		
None	16 (33.33)	3 (20)			
Grade 1-2	28 (58.33)	12 (80)			
Grade ≥3	4 (8.33)	0 (0)			
NT			1.000		
None	40 (83.33)	13 (86.67)			
Grade 1-2	5 (10.41)	2 (13.33)			
Grade ≥3	3 (6.25)	0 (0)			
Baseline ANC, $x10^9$/l [1.80-6.30]	2.86 (0.61-11.35)	4.31 (1.55-7.01)	0.005	0.504 (0.297-0.865)	0.011
Baseline hemoglobin, g/l [115-150]	106 (51-149)	127 (103-165)	<0.001	0.947 (0.899-0.998)	0.041
Baseline platelet count, $x10^9$/l [125-350]	157 (23-359)	212 (127-447)	0.158		
Baseline CRP, mg/l [0.0-5.0]	18.25 (0.40-200)	5.8 (0.4-114.70)	0.113		
Baseline ferritin, ng/ml [30-400]	613.60 (20-25822)	324.1 (33.10-830)	0.014	1.001 (0.998-1.004)	0.362
Baseline IL-6, pg/l [0.01-7.0]	12.31 (1.50-882)	4.24 (1.50-25)	0.004	1.06 (0.967-1.162)	0.211

Values are expressed as n (%) or the median (range). CRP, C-reactive protein; CAR-T, chimeric antigen receptor T-cell; ANC, absolute neutrophil count; CRS, cytokine release syndrome; NT, neurological toxicity; NK, natural killer; OR, odds ratio; HSCT, hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group.

CAR-T therapy, a univariate risk factor analysis was carried out. The results indicated that grade ≥3 cytopenia was not associated with sex, age, different CAR-T targets, times of prior chemotherapies, prior autologous HSCT, bone marrow involvement, CRS or NT. Of note, grade ≥3 cytopenia was associated with the Eastern Cooperative Oncology Group (ECOG) score, baseline ANC and hemoglobin concentration, and baseline ferritin and IL-6 levels. Grade ≥3 neutropenia was significantly associated with the ECOG score, baseline ANC and hemoglobin, and baseline IL-6 and ferritin. Anemia grade >3 was significantly associated with the ECOG score, baseline hemoglobin and platelet count, baseline IL-6 and ferritin, and baseline CRP. Thrombocytopenia grade >3 was significantly associated with the ECOG score, baseline hemoglobin and platelet count, baseline IL-6 and ferritin, baseline CRP and the severity of CRS (Tables SII-IV). The incidence of thrombocytopenia in patients with grade 1-2 CRS was 32.50% (13 cases) and this was significantly higher than that in patients without CRS (5.26%; 1 case). The incidence of thrombocytopenia in patients with grade ≥3 CRS was 25% (1 case) and this was higher than that in patients without CRS (5.26%), but the difference between groups was not statistically significant (Table SV). A binary logistic regression model was applied for multivariate risk factor analysis and the results indicated that only baseline ANC and hemoglobin levels were independently associated with grade ≥3 cytopenia (Table I).

Table II. Clinical characteristics of the hematologic recovery group and the unrecovered group at day +28.

Characteristic	Recovery group	Unrecovered group	P-value
Gender			1.0
Male	27 (69.23)	15 (71.42)	
Female	12 (30.76)	6 (28.57)	
Age, years	47 (23-72)	42 (21-68)	0.172
ECOG score	1 (0-3)	2 (0-3)	0.349
Number of prior chemotherapies, times	8 (3-26)	9 (3-25)	0.493
Prior autologous HSCT			0.278
Yes	1 (2.56)	2 (9.52)	
No	38 (97.43)	19 (90.47)	
Bone marrow involvement			0.114
Yes	3 (7.7)	5 (23.8)	
No	36 (92.3)	16 (76.2)	
Targets of CAR-T cells			0.599
CD19	8 (20.5)	2 (9.5)	
CD20	5 (12.8)	2 (9.5)	
CD19-CD20	15 (38.5)	8 (38.1)	
CD19-CD22	10 (25.6)	9 (42.9)	
CD19-NK	1 (2.6)	0 (0)	
CRS			0.796
None	12 (30.77)	6 (28.57)	
Grade 1-2	25 (64.10)	15 (71.43)	
Grade ≥3	2 (5.12)	0 (0)	
NT			0.193
None	34 (87.18)	17 (80.95)	
Grade 1-2	5 (12.82)	2 (9.52)	
Grade ≥3	0 (0)	2 (9.52)	
Baseline ANC, $x10^9$/l	3.61 (0.61-7.01)	1.77 (0.71-11.35)	0.004
Baseline hemoglobin, g/l	119 (77-165)	90 (51-147)	<0.001
Baseline platelet count, $x10^9$/l	200 (54-447)	151 (23-321)	0.016
Baseline CRP, mg/l	7.2 (0.40-128.90)	28.5 (1-200)	0.022
Baseline ferritin, ng/ml	426 (20-3,323)	774 (92.13-25,822)	0.012
Baseline IL-6, pg/l	5.88 (1.50-57)	22.25 (1.50-149.10)	0.003
Peak CRP, mg/l	63.30 (1.30-200)	91.3 (1.50-1,636)	0.048
Peak ferritin, ng/ml	542.40 (25.12-7,000)	1,396 (122.60-25,822)	0.003
Peak IL-6, pg/l	21.35 (4.06-102)	47.35 (5.02-1,453)	0.040

Values are expressed as n (%) or the median (range). CRP, C-reactive protein; CAR-T, chimeric antigen receptor T-cell; ANC, absolute neutrophil count; CRS, cytokine release syndrome; NT, neurological toxicity; NK, natural killer; HSCT, hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group.

Analysis of factors associated with hematologic recovery. A total of 60 patients were included in the follow-up at 28 days following CAR-T cell infusion, following the exclusion of 3 patients who died early. Patients were divided into recovered and unrecovered groups, according to whether the peripheral blood cell count was recovered. Among them, 21 patients (35%) exhibited no hematologic recovery and 39 patients (65%) exhibited hematologic recovery. Day +28 hemocyte recovery was analyzed in all patients and the results suggested that patients in the recovered group exhibited higher baseline blood cell counts, baseline IL-6, ferritin and baseline CRP levels. Of note, the peak levels of IL-6, ferritin and CRP also affected blood cell recovery. Univariate analysis demonstrated that sex, age, disease stage, different CAR-T targets, number of prior chemotherapies, autologous HSCT, bone marrow involvement, CRS and NT were not associated with hemocyte recovery at day +28 (Table II). ROC curve analysis was used to obtain the optimal cut-off values of baseline ANC, hemoglobin, baseline IL-6, baseline ferritin and peak ferritin (area under the curve, 0.7-0.9) (Fig. SI). Cut-off values were used to convert continuous variables into categorical variables. Univariate analysis indicated that the factors affecting hemocyte recovery were

Table III. Univariate and multivariate analysis of hematologic recovery at day +28.

	Univariate analysis		Multivariate analysis	
Variable	OR (95%CI)	P-value	OR (95%CI)	P-value
Baseline ANC <2.29x10^9/l	11 (3.130-38.660)	<0.001	14.834 (2.391-92.051)	0.004
Baseline hemoglobin <114.50 g/l	8.500 (2.371-30.466)	0.001	7.963 (1.323-47.921)	0.023
Baseline IL-6 >21.43 pg/l	0.107 (0.028-0.410)	0.001	0.091 (0.100-0.802)	0.031
Baseline ferritin >558.65 ng/ml	0.250 (0.081-0.770)	0.016	0.966 (0.098-9.525)	0.976
Peak ferritin >1195 ng/ml	0.110 (0.031-0.395)	0.001	0.456 (0.036-5.851)	0.546

ANC, absolute neutrophil count; OR, odds ratio.

baseline ANC, baseline hemoglobin, baseline IL-6, baseline ferritin and peak values of ferritin. Furthermore, the results of the multivariate analysis suggested that baseline ANC <2.29x10^9/l, baseline hemoglobin <114.5 g/l and baseline IL-6 >21.43 pg/l were independent influencing factors on hematologic recovery (Table III).

Discussion

As a novel cellular immunotherapy, CAR-T cells have achieved high response and remission rates in patients with relapsed and refractory hematological malignancies, including B-ALL, B-NHL and MM. Of note, numerous clinical guidelines recommend CAR-T cell therapy. Common adverse events associated with CAR-T therapy, including CRS and NT, are detailed in the previous literature (11,12). However, studies exploring potential factors associated with hematological toxicity, particularly in relapsed and refractory B-NHL, are lacking. The present study retrospectively analyzed the occurrence, recovery and risk factors of cytopenia in patients with relapsed and refractory B-NHL following CAR-T therapy.

In the phase II study ZUMA-1 (11), the incidence of grade >3 neutropenia, anemia and thrombocytopenia following CAR-T cell infusion was 78, 43 and 38%, respectively, in 111 patients with relapsed and refractory B-NHL. Fried *et al* (13) reported that the incidence of grade ≥3 neutropenia and thrombocytopenia was 72 and 28% in 38 patients with relapsed and refractory B-NHL and ALL, respectively, following CD19 CAR-T cell infusion. The present study suggested that patients with relapsed and refractory B-NHL experienced cytopenia following CAR-T cell infusion and the incidence of grade ≥3 neutropenia, anemia and thrombocytopenia was 76.19, 25.3 and 23.80%, respectively. The incidence of grade ≥3 neutropenia was comparable to the incidence observed in previous studies, while the incidence of grade ≥3 anemia and thrombocytopenia was lower. Cytopenia following CAR-T cell infusion is common and patients exhibit the highest incidence of grade ≥3 neutropenia. Thus, clinicians should closely monitor cytopenia following CAR-T cell infusion and treatment should be used to prevent infection, bleeding or anemia.

Results of previous studies suggested that cytopenia following the infusion of CAR-T cells is biphasic or triphasic, with the first phase occurring within 3-4 weeks. Such early cytopenia may be attributed to lymphodepletion regimens, bridging chemotherapy or radiotherapy carried out prior to CAR-T cell infusion, or severe CRS (14,15). Results of the present study demonstrated that the lowest time to cytopenia occurrence was 5-10 days following infusion. Furthermore, associated risk factors were analyzed in the present study and the results indicated that grade ≥3 cytopenia was not associated with primary disease stage, the number of prior chemotherapies, prior autologous HSCT, CRS or NT. However, grade ≥3 cytopenia was associated with the ECOG score, baseline blood cell levels and baseline inflammatory factor levels. The present study also determined the risk factors associated with grade ≥3 neutropenia, anemia and thrombocytopenia and the results demonstrated that the severity of CRS was associated with grade ≥3 thrombocytopenia. Through univariate analysis, Fried *et al* (13) revealed that the only risk factor associated with grade ≥3 anemia and thrombocytopenia was autologous HSCT within 1 year prior to CAR-T cell infusion. Patients with grade ≥2 CRS and low baseline blood cell levels exhibited a higher rate of grade ≥3 thrombocytopenia; however, these results were not statistically significant. Although the potential association between severe CRS and grade ≥3 cytopenia was not consistently reported among studies (13,14), close monitoring of patients and timely intervention are essential for clinicians.

To date, research has focused on the duration and mechanisms of cytopenia and results of previous studies demonstrated that prolonged cytopenia is associated with prognosis. However, the definition of prolonged cytopenia differed among studies. In the majority of previous studies (14,16), day +28 to day +42 following CAR-T cell infusion was usually set as a time node; however, other studies extended the time node to day +80 or day +90. The TRANSCEND NHL-001 trial (16) included 269 patients with relapsed and refractory B-NHL, 37% of whom experienced persistent cytopenia at day +29 following CAR-T cell infusion. Hockings *et al* (14) analyzed 39 patients with relapsed and refractory B-NHL and highlighted that 43% experienced persistent cytopenia at day +28 following CAR-T cell infusion. Furthermore, Nagle *et al* (17) reported that the 1-year overall survival (OS) rate of 31 patients with relapsed and refractory DLBCL who had experienced persistent cytopenia on day +30 following CAR-T cell infusion was 36%, while the 1-year OS rate of patients without prolonged cytopenia was 81% and this difference was statistically significant. Results of the present study demonstrated that 35% of patients with relapsed and refractory

B-NHL experienced prolonged cytopenia at day +28 following CAR-T cell infusion. Collectively, these results demonstrated that cytopenia may not be a result of pre-treatment-mediated myelotoxicity. However, the duration of clinical observations of persistent cytopenia following CAR-T cell infusion differed among the previously studies.

Risk factors reported for prolonged cytopenia associated with CAR-T cell therapy are varied, including a higher number of previous treatment lines, an increased median age, bone marrow reserves with baseline cell defects, severity of CRS, baseline and peak levels of various inflammatory cytokines and potential clonal hematopoiesis. Of note, research has predominantly focused on the severity of CRS, baseline bone marrow reserve, and baseline and peak levels of inflammatory cytokines. Strati *et al* (18) analyzed the risk factors associated with cytopenia at day +30 in 31 patients with relapsed and refractory B-NHL enrolled in the ZUMA-1 and ZUMA-9 trials. Of note, the results of this previous study demonstrated no association between the incidence of CRS and grade >3 NT. The present study did not indicate any association between severe CRS or NT with prolonged cytopenia, either; however, baseline blood count levels, baseline IL-6, ferritin, baseline CRP levels and the corresponding peak values were associated with prolonged cytopenia. In a multicenter retrospective study, Rejeski *et al* (19) analyzed hematological toxicity following CAR-T therapy in 258 patients with relapsed and refractory B-NHL, using day +60 as the study endpoint. The results of this previous study indicated that the incidence and severity of CRS and NT, the peak levels of cytokines and the number of previous treatments were not associated with prolonged cytopenia, while baseline thrombocytopenia and methemoglobinemia were risk factors. These results suggested that bone marrow reserves and inflammatory state prior to CAR-T therapy are key features of prolonged cytopenia. Of note, bone marrow reserves may be impacted by local inflammatory factors, such as IL-6 signaling involved in hematopoietic stem cell development.

The present study is limited by being a retrospective single-center study with incomplete data, including a lack of the expansion of CAR-T cells. Furthermore, only the changes and recovery of blood cells at day +28 were analyzed, and they were not observed for a longer period of time. In addition, the relationship between cytopenia and clinical prognosis was not analysed. Considering the influence of basic cytokines on blood cell recovery, the mechanism of their influence may be further explored and the prediction model may be established.

Collectively, the results of the present study suggested that prolonged cytopenia occurred in patients following CAR-T cell therapy and patients also experienced a high incidence of CAR-T-associated hematologic toxicity. Furthermore, the risk factors associated with prolonged cytopenia were bone marrow reserves and baseline levels of inflammatory factors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TQ designed the study and wrote the manuscript. LH and YZ primarily wrote the manuscript and prepared the tables. LH, YZ, YW and SM made substantial contributions to the acquisition and analysis of data. DL, ZL and KX made contributions to the analysis and interpretation of data and revised the manuscript. TQ and LH checked and confirmed the authenticity of the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Xuzhou, China; nos. XYFY2017-KL009-01, XYFY2018-KL013-01 and XYFY2020-KL080-01). Patients provided written informed consent prior to sample collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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