Nutritional status alterations after chimeric antigen receptor T cell therapy in patients with hematological malignancies: a retrospective study

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Abstract
Purpose The influence of innovative chimeric antigen receptor T cell (CAR-T) therapy for hematological malignancies on nutritional status remains unknown. Therefore, we aim to explore the alterations of nutritional status after CAR-T cell therapy in patients with hematological malignancies.

Methods We retrospectively collected the data of patients with acute leukemia (AL), lymphoma, and multiple myeloma (MM), who underwent CAR-T therapy at our hospital from 2018 to 2020. The serum albumin, triglyceride, and cholesterol before and 7, 14, and 21 days after CAR-T cell infusion were compared and analyzed.

Result A total of 117 patients were enrolled, consisting of 39 AL, 23 lymphoma, and 55 MM patients. The baseline albumin, triglyceride, and cholesterol were 37.43 ± 5.08 mg/L, 1.63 ± 0.74 mmol/L, and 3.62 ± 1.03 mmol/L, respectively. The lowest albumin level was found at 7 days after CAR-T cell infusion compared with baseline (P < 0.001), while the levels of triglyceride increased at 14 and 21 days (P < 0.001, P = 0.036). The levels of cholesterol at 7, 14, and 21 days after CAR-T cell infusion were lower than baseline (all P < 0.05). Spearman’s correlation coefficient showed cytokine release syndrome grade was negatively correlated with the levels of albumin at 7 days and cholesterol at 21 days after CAR-T cell infusion (r = −0.353, P < 0.001; r = −0.395, P = 0.002).

Conclusion The alterations of different nutrition-related biochemical parameters varied after CAR-T cell therapy. The levels of albumin and total cholesterol after CAR-T cell infusion were negatively correlated with the grade of cytokine release syndrome. Specific screening and intervention for malnutrition in patients receiving CAR-T cell therapy need to be explored in further studies.

Keywords Nutritional status · CAR-T therapy · Hematological malignancies · Cytokine release syndrome

Introduction
Since the first batch of chimeric antigen receptor T (CAR-T) cells were approved by the Food and Drug Administration (FDA) in the USA in 2017 [1–3], CAR-T therapy has achieved great progress and became a promising approach for cancers, especially in relapsed or refractory (r/r) hematological malignancies [4, 5]. In July 2020, FDA approved another CAR-T cell drug named Tecartus for treatment of adult patients diagnosed with mantle cell lymphoma (MCL). Adverse events, such as cytokine release syndrome (CRS) and tumor lysis syndrome, still are the main challenges in the clinical application of CAR-T cell [6, 7]. Though CAR-T cell therapy as an innovative treatment has the potential to be a dominated alternative for patients with hematological
malignancies, the effectiveness and safety need to be determined in further studies [8].

Malnutrition may occur in 30 to 80% of patients with cancer [9, 10]. Nausea, diarrhea, constipation, and fatigue induced by chemotherapy or antineoplastic therapy and cachexia due to tumor-related metabolism abnormalities [11, 12] might eventually lead to malnutrition. It commonly manifested as weight loss, reduced muscle mass or body mass index (BMI), abnormalities in biochemical indices, or ongoing high activity of inflammation. Studies have validated the effectiveness of various nutrition-related indices, such as acute-phase reaction proteins (including albumin and immunoglobulin) [13], biochemical parameters (including blood lipids, glucose and blood glucose, and electrolytes), and calculated indices (including neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio) [14]. In addition, nutrition status evaluation scales, such as Patient-Generated Subjective Global Assessment [15], have been widely applied in clinical practice. As a key step in identifying cancer patients with malnutrition, nutrition screening provides the possibility of subsequent specific nutritional guidance or intervention.

Malnutrition in cancer patients has been proven to reduce response to treatment and increase treatment-associated side effects [16], as well as influence on the quality of life, infection, relapse rate, longer hospital stays, and higher healthcare costs [17–20]. Furthermore, being a major cause of cancer death, malnutrition could predict poor prognosis of patients [21]. Multiple studies have proven the relationships between malnutrition, metabolism, and immunity, especially concerning T cells [22, 23]. Regarding the crucial role of T cells in the effectiveness and safety of CAR-T therapy, the exploration of nutrition status alteration after CAR-T cell infusion is needed.

Since no studies have reported on the changes of nutrition status after CAR-T cell therapy, we aim to investigate the alterations of nutritional status after CAR-T cell therapy in patients with hematological malignancies in the present study and provide evidence for nutrition screening and intervention in such patients.

Methods

Study design and patients’ selection

We retrospectively reviewed 117 patients who enrolled in phase 1/2 CAR-T cell therapy clinical trials conducted at our center from 2018 to 2020. Thirty-nine patients with acute lymphoblastic leukemia (ALL) were enrolled in CAR-T cell therapy either targeting CD19 (ChiCTR-ORN-16008948) or CD19/CD22 (ChiCTR1800015575), and 23 patients with non-Hodgkin’s lymphoma (NHL) were treated with CD19-targeted CAR-T cell therapy (ChiCTR-OIC-17011310); moreover, 55 patients with multiple myeloma (MM) were administered with BCMA CAR-T cell (ChiCTR1800017404). These clinical trials were approved by the Medical Ethics Committee of the First Affiliated Hospital of Medical College, Zhejiang University, and performed according to the ethical principles of the Declaration of Helsinki.

The inclusion criteria were as follows: (1) age less than 75 years; (2) r/r B-cell hematological malignancies, including CD19 positive ALL, CD19 positive diffuse large B-cell lymphoma or follicular lymphoma, BCMA positive MM; (3) relapse after hematopoietic stem cell transplantation (HSCT) without evidence of graft-versus-host disease and not requiring immnosuppression therapy; (4) measurable disease. The exclusion criteria were as follows: (1) patients with inadequate hepatic and renal function; (2) patients with Eastern Cooperative Oncology Group performance status more than 2; (3) incomplete data. All patients were voluntarily participating in these trials and signed the informed consent form, and the informed consents were waived by the retrospective nature of this study.

Clinical protocol of CAR-T cell therapy

The protocol of CAR-T cell therapy was described previously [24]. Briefly, peripheral blood mononuclear cells were obtained from patients or donors by leukapheresis for CAR-T cell generation. T cells were transfected with CARs containing 4-1BB domain using lentivirus. Before CAR-T cell infusion, all patients received fludarabine- (30 mg/m² on days −4 to approximately −2) and Cy- (750 mg/m² on days −3 to approximately −2) based lymphodepletion regimen. The expansion and persistence of CAR-T cells were evaluated by flow cytometry and morphological analysis, and CAR DNA copy number was used as a complementary method.

Assessment of toxicities and efficacy

The grading of CRS was referred to a novel grading scale [25, 26], while other toxicities, including neurotoxicity and hematological toxicities, were assessed referring to the National Institutes of Health Common Terminology Criteria for Adverse Events Version 5.0 (http://ctep.cancer.gov/). On day 28, the response of CAR-T cell therapy would be evaluated.

Data collection

The baseline data, including age, gender, BMI, smoking history, hypertension, diabetes and HBV infection, residence, and care-giver, were collected. Nutritional status-related
parameters, including triglyceride, cholesterol, and albumin, were collected on the day of CAR-T cell transfusion and 7, 14, and 21 days after infusion.

**Statistical analysis**

SPSS 24.0 (SPSS Software Inc., Chicago, IL, USA) was used for statistical analyses, and GraphPad Prism 9.0.0 (San Diego, CA, USA) was used to draw the graphs. The continuous variables were presented as mean ± standard deviation and median (range). The categorical variables were presented as number (percentage). The parameters of multiple timepoints were compared by analysis of variance for repeated measurement. Mauchly’s test was used to determine whether the data were in line with the spherical hypothesis, and the Greenhouse–Geisser method was used for correction. Spearman’s correlation coefficient was used to analyze the correlation of serum albumin, triglyceride, and total cholesterol with CRS. \( P < 0.05 \) was considered significant.

**Results**

**Patients’ characteristics**

Among the 117 enrolled patients, the median age was 53 years (range, 14 to 74 years) with a BMI of 22.5 ± 2.8 kg/m², and the majority were male (56.4%). The patients were mostly married (91.5%) and half of them came from urban residence. Nearly 80% patients received cares from spouses during hospitalization. The baseline demographics characteristics are summarized in Table 1.

Thirty-nine patients (33.3%) were diagnosed with acute leukemia, 23 (19.7%) with lymphoma, and 55 (47.0%) with multiple myeloma, among which 33 (28.2%) had a history of hematopoietic stem cell transplantation (HSCT). Twenty-one patients complicated with hypertension and 14 with diabetes. Hepatitis B virus infection was found in 13 individuals (11.1%). The median length of hospital stay was 26 days (range, 7–90).

**Alterations of serum albumin**

The baseline albumin concentration was 37.43 ± 5.08 mg/L. The prevalence of hypoalbuminemia was 35.9% (42/117) at baseline. The level of albumin concentration was 34.12 ± 5.46 mg/L at 7 days after CAR-T cell infusion, which was significantly lower than baseline (mean difference: −3.84 mg/L, \( P < 0.001 \), Fig. 1). The prevalence of hypoalbuminemia (<35 mg/L) was 59.8% (70/117). Subsequently, it increased to 37.89 ± 4.99 and 38.45 ± 5.46 mg/L.

| Table 1 Characteristics of patients | Total (n=117) |
|-------------------------------------|--------------|
| Age, years, median (range)          | 53 (14–74)   |
| Male, n (%)                         | 66 (56.4)    |
| BMI, kg/m², mean ± SD               | 22.5 ± 2.8   |
| Residence, n (%)                    |              |
| Urban                               | 59 (50.4)    |
| Suburb                              | 27 (23.1)    |
| Rural                               | 31 (26.5)    |
| Married status, n (%)               |              |
| Unmarried                           | 10 (8.5)     |
| Married                             | 107 (91.5)   |
| Highest education, n (%)            |              |
| High school and below               | 89 (76.1)    |
| College and above                   | 26 (22.2)    |
| Missing data                        | 2 (1.7)      |
| Care giver, n (%)                   |              |
| Wife                                | 62 (53.0)    |
| Husband                             | 36 (30.8)    |
| Offspring                           | 8 (6.8)      |
| Parent                              | 11 (9.4)     |
| Diagnosis, n (%)                    |              |
| Acute leukemia                      | 39 (33.3)    |
| Lymphoma                            | 23 (19.7)    |
| Multiple myeloma                    | 55 (47.0)    |
| Chemotherapy cycle, median (range)  | 7 (1–70)     |
| History of HSCT, n (%)              |              |
| Yes                                 | 33 (28.2)    |
| No                                  | 83 (70.9)    |
| Missing data                        | 1 (0.9)      |
| Smoking history, n (%)              |              |
| Yes                                 | 20 (17.1)    |
| No                                  | 97 (82.9)    |
| Drinking history, n (%)             |              |
| Yes                                 | 20 (17.1)    |
| No                                  | 97 (82.9)    |
| Diabetes, n (%)                     |              |
| Yes                                 | 14 (12.0)    |
| No                                  | 102 (87.1)   |
| Missing data                        | 1 (0.9)      |
| Hypertension, n (%)                 |              |
| Yes                                 | 21 (17.9)    |
| No                                  | 95 (81.2)    |
| Missing data                        | 1 (0.9)      |
| HBV infection, n (%)                |              |
| Yes                                 | 13 (11.1)    |
| No                                  | 104 (88.9)   |
| Baseline ALB, mg/L, mean ± SD       | 37.43 ± 5.08 |
| Baseline TG, mmol/L, mean ± SD      | 1.63 ± 0.74  |
| Baseline TC, mmol/L, mean ± SD      | 3.62 ± 1.03  |
| Hospital stay, days, median (range) | 26 (7–90)    |

SD, standard deviation; HSCT, hematopoietic stem cell transplantation; HBV, hepatitis B virus; ALB, albumin; TG, triglycerides; TC, total cholesterol
Alterations of serum triglyceride

The level of triglyceride at 7 days after CAR-T therapy was 1.68 ± 1.23 mmol/L, which was similar with baseline (1.63 ± 0.74 mmol/L, P > 0.999). Nevertheless, it increased at 14 days (2.21 ± 0.98 mmol/L, mean difference: 0.67 mmol/L, P < 0.001, Fig. 2) and remained at a high level at 21 days after CAR-T cell infusion (2.14 ± 1.63 mmol/L, mean difference: 0.43 mmol/L, P = 0.036). The prevalence of hypertriglyceridemia (>1.81 mmol/L) was 53.8% (63/117) at 14 days after CAR-T cell infusion.

Alterations of serum total cholesterol

The baseline total cholesterol concentration was 3.62 ± 1.03 mmol/L. The lowest level was found at 7 days after CAR-T cell infusion (2.78 ± 0.91 mmol/L, mean difference: −0.85 mmol/L, P < 0.001, Fig. 3). The prevalence of hypocholesterolemia was 91.5% (107/117). The total cholesterol concentration slightly increased at 14 and 21 days (2.98 ± 0.84 mmol/L and 3.14 ± 1.00 mmol/L, respectively), although the differences compared with baseline remained significant (mean difference: −0.79 mmol/L, P < 0.001; mean difference: −0.47 mmol/L, P = 0.003).

Correlation of serum albumin, triglyceride, and total cholesterol with CRS

Thirty-five patients (30.0%) had grade 0 or grade 1 CRS, while 47 (40.1%) developed grade 2 CRS and 28 (23.9%)
developed grade 3 CRS. Notably, 6 patients (5.1%) experienced a grade 4 CRS but no death occurred.

Spearman’s correlation coefficient showed that CRS was negatively correlated with the level of serum albumin at 7 days ($r = -0.353, P < 0.001$) and 14 days ($r = -0.292, P = 0.003$), but not 21 days after CAR-T infusion ($r = -0.104, P = 0.421$). Moreover, the negative correlations were found between total cholesterol levels and CRS at 7, 14, and 21 days after CAR-T therapy ($r = -0.216, P = 0.025; r = -0.310, P = 0.002; r = -0.395, P = 0.002$, respectively). However, no correlations were between triglyceride and CRS (all $P > 0.05$). The details are presented in Table 2.

### Discussion

In this retrospective study, the changes of nutritional status after CAR-T therapy were preliminarily explored. The finding showed the alterations vary across different indices, where serum albumin and total cholesterol decreased at the lowest level 7 days after CAR-T cell infusion, while the level of triglyceride increased at 14 and 21 days after CAR-T cell infusion.

The prevalence of hypoalbuminemia was 35.9% at baseline in this study, which was within the range of 30–45% in previous studies based on hematological malignancies population [27–29]. In addition, the prevalence of hypocholesterolemia was 91.5% in this study, even higher than a previous study reported [30]. Recently, a retrospective study including advanced hepatocellular carcinoma patients receiving anti-PD-1 immunotherapy reported that serum albumin concentration decreased distinctly after immunotherapy in disease progression patients [31]. In this study, the lowest level of serum albumin and TC concentration was found 7 days after CAR-T cell infusion and steadily climbed back. Meanwhile, the level of TG after chemotherapy increased compared with pre-therapy [32, 33], which is similar in the present study. Researchers have reported the influence of cytokines on the diet and metabolism of cancer patients [34, 35]. Cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF-α) together lead to decrease intake of food, increase glucose oxidation, increase synthesis of acute phase reactive proteins, decrease fatty acid uptake, and increase resting energy expenditure, meanwhile, affecting metabolism by altering insulin, glucagon, and corticosterone levels [35]. As studies revealed the onset-time of CRS was around 7–14 days [36], we supposed the decrease of albumin and TC to be correlated with CRS somehow. Subsequently, correlation analysis in this study showed negative correlations between serum albumin and total cholesterol with CRS, which preliminarily support the assumption. Further studies with larger sample size and concerning the mechanism of the influence of CRS on nutrition status are needed.

The effect of malnutrition on immunity remains appealing whether in cancer patients or healthy population. Relevant animal experiments proved that malnutrition could lead to a decrease in immune cells, especially T cells [22]. Similar findings were seen in human studies. Malnourished children had decreased CD4+ and CD8+ T cell numbers in whole blood compared to well-nourished children [37]. Yilmaz et al. [28] investigated the predictive performance of biochemical parameters in hematological malignancies patients and results suggested that serum albumin was a reliable index, which was supported by other studies [38, 39]. Moreover, an observation study reported that lower albumin concentration pre-treatment was associated with toxic induction deaths after chemotherapy in pediatric ALL patients [29]. Fang et al. [31] revealed the correlation between serum albumin and the efficacy of anti-PD-1 immunotherapy, though the correlation was partial due to the small sample size. Nevertheless, the significant association of the level of serum albumin concentration and the prognosis of patients receiving CAR-T cell therapy was not found in our studies. We considered the frequent screening and active intervention might eliminate the effect, not to mention the small sample size and short follow-up.

The study had several limitations. Firstly, due to its retrospective nature, the selected bias and incomplete data were inevitable. In addition, limited follow-up data lead to the difficulty in exploring the effect of malnutrition on the prognosis of patients. Secondly, the sample size was relatively small, which might result in the failure in the investigation of the risk factor of malnutrition. Finally, the evaluation of nutrition status

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**Table 2 Correlation of serum albumin, triglyceride, and total cholesterol with cytokine release syndrome**

| Parameter                  | $r$    | $P$    |
|----------------------------|--------|--------|
| Albumin                    |        |        |
| Baseline                   | −0.184 | 0.049  |
| 7 days after CAR-T cell infusion | −0.353 | <0.001 |
| 14 days after CAR-T cell infusion | −0.292 | 0.003  |
| 21 days after CAR-T cell infusion | −0.104 | 0.421  |
| Triglyceride               |        |        |
| Baseline                   | 0.014  | 0.884  |
| 7 days after CAR-T cell infusion | 0.164  | 0.089  |
| 14 days after CAR-T cell infusion | −0.017 | 0.868  |
| 21 days after CAR-T cell infusion | −0.083 | 0.534  |
| Total cholesterol          |        |        |
| Baseline                   | 0.004  | 0.970  |
| 7 days after CAR-T cell infusion | −0.216 | 0.025  |
| 14 days after CAR-T cell infusion | −0.310 | 0.002  |
| 21 days after CAR-T cell infusion | −0.395 | 0.002  |

$P < 0.05$ was considered significant. Bold values were considered significant.
in this study was insufficient. The application of other nutrition screening methods, such as muscle mass index, Patient-Generated Subjective Global Assessment, and Nutrition Risk Index, should be explored in further studies.

In conclusion, the alterations of different nutrition-related biochemical parameters varied after CAR-T cell therapy. Our findings revealed that serum albumin and total cholesterol concentration decreased at the lowest level 7 days after CAR-T cell infusion, while triglyceride increased at 14 and 21 days after CAR-T cell infusion. The levels of albumin and total cholesterol after CAR-T cell infusion were negatively correlated with cytokine release syndrome. Specific screening and intervention for malnutrition in patients receiving CAR-T cell therapy need to be explored in further studies.

Author contribution Shuyi Ding, Lingxia Cai, Aiyun Jin, Xiaoyu Zhou, Jiali Yan, and Tingting Wang designed the study and collected the data. Linqin Wang and Houli Zhao analyzed the data and wrote the manuscript. Yongxian Hu proofread the manuscript.

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Availability of data and material Data is available on request.

Code availability Not applicable.

Declarations

Ethics approval These clinical trials were performed according to the ethical principles of the Declaration of Helsinki. Approval was granted by the Medical Ethics Committee of the First Affiliated Hospital of Medical College, Zhejiang University (ChiCTR-ORN-16008948, ChiCTR1800015575, ChiCTR-OIC-17011310, ChiCTR1800017404).

Consent for publication Obtained.

Conflict of interest The authors declare no competing interests.

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