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Role of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Predicting the Adverse Effects of Chimeric Antigen Receptor T Cell Therapy in Patients with Non-Hodgkin Lymphoma

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CD19-targeting chimeric antigen receptor (CAR)-T cell therapy has shown great efficacy in patients with relapsed/refractory non-Hodgkin lymphoma (NHL) but has been associated with serious adverse effects, such as cytokine release syndrome (CRS). It has been speculated that NHL baseline disease burden might affect clinical outcome and CRS, but this has not been explored in detail in any previous study. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG), as measured by fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET-CT), are quantitative indicators of baseline tumor burden. Using FDG PET-CT, we calculated baseline and post-CAR-T cell therapy MTV and TLG in 19 patients with NHL. The median MTV was 72 cm^3 (range, .02 to 1137.7 cm^3), and the median TLG was 555.9 (range, .011 to 8990.3). After a median follow-up of 5 months (range, 1 to 12 months), the best overall response rate was 79.0%. The baseline MTV and TLG did not differ significantly between patients with response and those without response (P = .62 and .95, respectively). On Cox regression analysis, baseline MTV and TLG were not significantly associated with overall survival (P = .67 and .45, respectively). Patients with mild and moderate CRS (grade 0 to 2) had significantly lower MTV and TLG than those with severe CRS (grade 3 to 4) (P = .008 for MTV comparison, P = .011 for TLG comparison). Using FDG PET-CT, we also demonstrated that CAR-T cell therapy in patients with NHL was associated with pseudoprogression and local immune activation. Our data indicate that patients with higher baseline disease burden have more severe CRS, and that CAR-T cell therapy is associated with lymphoma pseudoprogression and local immune activation.

INTRODUCTION

Chimeric antigen receptor (CAR)-T cell therapy has achieved great success in recent years, demonstrating a high complete remission (CR) rate and durable response in patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL) [1,2]. However, CAR-T cell therapy is associated with unique adverse effects, such as cytokine release syndrome (CRS) and CAR-T cell-related neurologic toxicities [3]. Moreover, infiltration of CAR-T cells with concurrent local inflammation can cause damage to affected organs; for example, we previously reported a case of severe pleural effusion in a patient with pleural involvement [4]. Therefore, developing methods to predict the occurrence and severity of adverse effects is an important area of research.

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET-CT) is commonly used for the diagnosis, staging, and evaluation of response in patients with non-Hodgkin lymphoma (NHL). This imaging technique is highly sensitive for determining sites of disease; in addition, the residual signal after therapy is predictive of long-term survival in chemotherapy [5,6]. Moreover, quantitative measurement of baseline metabolic tumor burden as metabolic tumor volume (MTV) or total lesion glycolysis (TLG) has shown significant prognostic value in patients with NHL treated with chemotherapy [7-9].

For CAR-T cell therapy in patients with acute lymphoblastic leukemia (ALL), studies have confirmed the relationship between baseline disease burden and the severity of adverse effects, as well as long-term outcomes [10]. However, such a relationship has yet to be explored in NHL. In this retrospective

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study, by comparing the baseline MTV and TLG before and after CAR-T cell infusion, we investigated the role of baseline FDG PET-CT in predicting the adverse effects and prognosis of CAR-T cell therapy.

METHODS

Patients and Data Collection

We retrospectively reviewed patients with NHL who received CD19-targeting CAR-T cell therapy at our center between March 2017 and July 2018. The study was conducted according to the ethical principles for medical research involving human subjects as stated in the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Zhejiang University. All participants provided signed informed consent for participation.

Data were extracted from the electronic medical record system and the imaging system. The grading of CRS was based on the Penn grading scale [11]. The grading of neurotoxicity was based on the Common Terminology Criteria for Adverse Events.

CD19-Targeting CAR-T Cell Therapy

The protocol for CD19-targeting CAR-T cell therapy at our center has been described previously [12]. In brief, peripheral blood mononuclear cells were obtained from patients or donors by leukapheresis for CAR-T cell production. T cells were transfected with CARs containing the 4-1BB domain using lentivirus. All patients received a fludarabine (30 mg/m^2 on days -4 to -2) and Cy (750 mg/m^2 on day -2)-based lymphodepletion regimen before CAR-T cell infusion.

Imaging Acquisition and Calculation of Metabolic Parameters

^{18}F-FDG was synthesized with a Siemens Eclipse cyclotron (Siemens Medical Solutions, Knoxville, TN) and an FDG4 chemical module. Patients were kept on nil per os for 6 hours before ^{18}F-FDG injections, with a dose of 4.44 to 5.55 MBq/kg. Images were acquired using a Siemens PET/CT Biograph 16 (Siemens Medical Solutions). The evaluation of tumor response was based on the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), given that lymphoma lesions were measured quantitatively in our study. Two experienced radiologists independently reviewed all images. MTV and TLG were calculated using the Syngo volume-counting program (Siemens Medical Solutions).

Statistical Analysis

Comparisons among the groups were performed using the chi-square test or Fisher exact test as appropriate for categorical variables and the Mann-Whitney *U* test for continuous variables. The time of the first CAR-T cell infusion served as the origin in all the time-to-event analyses. The analysis of overall survival (OS) used death as the event; the analysis of event-free survival used the earliest of no response, relapse, or death as the event; and the analysis of relapse-free survival used relapse as the event. Patients without an event had their data censored for the last follow-up. Estimates and 95% confidence intervals (CIs) for OS and event-free survival were calculated using the Kaplan-Meier method and compared using the log-rank test. Binomial proportion confidence interval was calculated using the Clopper-Pearson method. All *P* values represented were 2-sided, and results were considered statistically significant at $P < .05$. Statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY), and graphs were prepared using SigmaPlot version 12.0 (Systat Software, San Jose, CA). Complete data are available from the corresponding authors on reasonable request.

RESULTS

Patient Baseline Characteristics

A total of 19 patients received CD19-targeting CAR-T cell therapy during the study period. The baseline characteristics of these 19 patients are summarized in Table 1. Twelve males and 7 females were enrolled in the study. The median age was 43 years (range, 22 to 67 years). In terms of histological type, 14 patients had DLBCL, 3 patients had follicular lymphoma, 1 patient had mucosa-associated lymphoid tissue lymphoma, 1 patient had Burkitt lymphoma, and 1 patient had ovarian lymphoblastic lymphoma. The median number of previous lines of therapy was 4 (range, 2 to 6). Five patients (26.3%) had undergone previous hematopoietic stem cell transplantation. For patients with DLBCL, 12 (85.7%) patients had an International Prognostic Index score ≥2. CAR-T cell dose varied considerably among the patients, with a median dose of 5.1×10^6/kg, ranging from 1.1×10^6/kg to 32.7×10^6/kg. The patients also had a wide range of baseline disease burden, with a median MTV of 72 cm^3 (range, 0.02 to 1137.7 cm^3) and a median TLG of 555.9 (range, 0.011 to 8990.3).

Baseline Tumor Metabolic Burden and Treatment Outcomes

The changes in MTV in our patients are shown in Figure 1A. All patients underwent FDG PET-CT evaluation before the CAR T-cell infusion (PET-0) and a repeat FDG PET-CT scan at 1 month after the infusion (PET-1). Some patients had follow-up FDG PET-CT scan at the second month (PET-2) and third month (PET-3) after CAR T-cell infusion. After a median follow-up of 5 months (range, 1 to 12 months), the best overall response rate was 79.0% (95% CI, 54.4% to 94.0%), with 7 patients (36.9%; 95% CI, 16.3% to 61.6%) achieving complete remission (CR) and 8 patients achieving partial remission (PR). The same response rates were obtained when we assessed response rates using the Lugano criteria. For patients who responded, the median baseline MTV was 58.1 cm^3 (range, .05 to 789.1 cm^3), which was not significantly different from that of patients without a response (median, 110.8 cm^3; range, .02 to 1137.7 cm^3; *P* = .62). Likewise, the median TLG did not differ significantly between patients who responded and those who did not respond (616.4 versus 525.6; *P* = .95). The median OS was 9.8 months (95% CI, 7.3 to 12.4 months), with 8.6 months (95% CI, 5.6 to 11.5 months) in patients with MTV above the median and 11.5 months (95% CI, 8.5 to 14.5 months) in patients with MTV below the median (*P* = .35) (Figure 1B). On Cox regression analysis, neither baseline MTV nor baseline TLG was significantly associated with OS (*P* = .67 and .45, respectively).

Baseline Tumor Metabolic Burden and Adverse Effects

The most common adverse effect of CAR-T cell therapy is CRS. Presenting with high fever, hypotension, and multiorgan toxicity, CRS is triggered by activation of CAR-T cells and bystander immune cells. It is characterized by increased levels of various cytokines, including CAR-T cell-derived INF-γ and IL-2 and monocyte-derived IL-6 and IL-1 [13,14]. In our cohort, 8 patients (42.1%) had grade 0 or 1 CRS, 7 patients (36.8%) had grade 2 CRS, and 4 patients (21.1%) had grade 3 CRS.

We explored the relationship between metabolic tumor burden and the severity of CRS. For patients with grade 0 or 1 CRS, the median MTV was 19.1 cm^3 (95% CI, .02 to 222.3 cm^3), and the median TLG was 78.3 (95% CI, .01 to 2176.2). For patients with grade 2 CRS, the median MTV was 99.5 cm^3 (95% CI, 21.4 to 488.6 cm^3), which was not significantly different from that in patients with grade 0 or 1 CRS (*P* = .23). Similarly, the median TLG was 540.8 (95% CI 64.6 to 2812.8), again not significant different from that in patients with grade 0 or 1 CRS (*P* = .53). For patients with grade 3 CRS, the median MTV was 528.2 cm^3 (95% CI, 165.8 to 1137.7 cm^3), significantly higher than that in patients with grade 0 or 1 CRS (*P* = .008), and the median TLG was 5844.5 (95% CI, 921.3 to 9384.0), also significantly higher than that in patients with grade 0 or 1 CRS (*P* = .016). The median baseline MTV in patients with non-severe CRS (grade 0 to 2) was 40.4 cm^3 (95% CI, .02 to 488.6 cm^3), significantly lower than that in patients with severe CRS (grade 3 or 4) (median, 528.1 cm^3; 95% CI, 165.8 to 1137.7 cm^3; *P* = .008). Similarly, the baseline TLG was significantly lower in patients with non-severe CRS compared with those with severe CRS (232.5 versus 5844.5; *P* = .011) (Figure 1C and D).

We next evaluated the use of the IL-6 antagonist tocilizumab, a specific medication for CRS, in our patients. The median MTV was significantly higher in the patients receiving tocilizumab compared with those not receiving tocilizumab (789.1 cm^3 versus 49.3 cm^3; *P* = .037). The median TLG in patients

Table 1
Baseline Patient Characteristics

Patient	Sex	Age, yr	Histology Type	Refractory Type	Ann Arbor Staging	IPI Score	Previous Lines of Therapy	CAR T Cell Dose, × 10^6/kg	Baseline MTV, cm^3	Baseline TLG
1	Male	39	DLBCL	Refractory to second-line	1	0	4	6.4	.05	.029
2	Male	51	MALToma	Refractory to second-line	2	NA	2	4.5	.06	.034
3	Female	62	DLBCL	Primary refractory	4	3	3	10.0	19.6	89.6
4	Male	51	DLBCL	Primary refractory	2	1	2	1.6	267.2	2698.7
5	Male	33	DLBCL	Primary refractory	4	3	3	32.7	149.6	1421.2
6	Female	32	Ovarian LBL	Relapse after auto-HSCT	3	NA	4	3.2	21.4	64.6
7	Female	27	DLBCL	Primary refractory	4	3	4	5.1	141.5	622.6
8	Female	43	DLBCL	Relapse after auto-HSCT	4	3	3	8.7	72.0	525.6
9	Female	22	DLBCL	Primary refractory	3	3	4	10.1	58.1	610.1
10	Male	35	DLBCL	Primary refractory	4	3	4	1.6	1137.7	9384.0
11	Male	35	DLBCL	Relapse after auto-HSCT	3	3	4	14.6	488.6	2812.8
12	Male	50	DLBCL	Refractory to second-line	4	3	3	6.3	789.1	8990.3
13	Female	43	DLBCL	Relapse after auto-HSCT	4	2	4	8.0	19.1	78.3
14	Male	40	DLBCL	Relapse after auto-HSCT	4	3	5	1.1	.02	.011
15	Male	55	BL	Refractory to second-line	4	NA	2	2.9	40.4	232.5
16	Male	67	DLBCL	Primary refractory	4	4	6	15.6	165.8	921.3
17	Male	65	DLBCL	Primary refractory	4	4	2	4.5	222.3	2176.2
18	Female	29	FL	Primary refractory	3	NA	5	5.0	.02	.088
19	Male	43	FL	Refractory to second-line	1	NA	6	4.9	127.1	555.9

IPI indicates International Prognostic Index; MALToma, mucosa-associated lymphoid tissue lymphoma; NA, not applicable; LBL, lymphoblastic lymphoma; auto-HSCT, autologous hematopoietic stem cell transplantation; BL, Burkitt lymphoma; FL, follicular lymphoma.

receiving tocilizumab was 8990.3, compared with 394.2 in those not receiving tocilizumab (P = .083).

Neurologic toxicity is the second most common adverse effect of CAR-T cell therapy. In our cohort, 4 patients (21.1%) developed neurologic toxicities. The median MTV in patients with neurologic toxicity was 72.0 cm^3 (95% CI, .02 to 789.1 cm^3), which was not significantly different than that in patients who did not experience neurologic toxicity (92.7 cm^3; 95% CI, .02 to 1137.7 cm^3; P = 1.00). The median TLG did not differ significantly between patients with neurologic toxicity and those without neurologic toxicity (555.9 cm^3 [95% CI, 0.03 to 8990.3 cm^3] versus 505.5 cm^3 [95% CI, .01 to 9384.0 cm^3]; P = 1.00).

Baseline Tumor Metabolic Burden and Local Complications

For CD19-targeting CAR-T cell therapy, an adverse effect unique to NHL but not ALL is local complications. Recruitment of CAR-T cells and non-CAR-T cells with concurrent immune activation can cause severe inflammation around local tissues [15].

Pseudoprogression, a well-defined phenomenon in other immunotherapies for solid tumors, is characterized by initial enlargement of tumors due to immune cell infiltration. It usually occurs within 6 to 12 weeks after the initiation of checkpoint inhibitors and is associated with favorable outcomes [16]. In our cohort, 3 patients had early and significant enlargement of lymphoma followed by rapid regression, mostly consistent with pseudoprogression. The enlargement caused local compression, leading to unexpected complications. In patient 4, a 51-year-old man with DLBCL transformed from follicular lymphoma, an FDG PET-CT scan performed 1 month before CAR T-cell therapy revealed multiple lymph nodes with metabolic activity surrounding the abdominal aorta, left diaphragm, and mesenteries. The largest mass was found behind the abdominal aorta, with a maximum standardized uptake value (SUVmax) of 18.1, an MTV of 267.2 cm^3, and a TLG of 2698.7. Five days after CAR-T cell infusion, the patient complained of increasing abdominal and back pain. An emergent abdominal CT scan revealed a markedly enlarged mass behind the aorta compared with a preinfusion CT scan obtained 11 days earlier (from 7.5 cm × 6.4 cm to 12.3 cm × 6.9 cm). The abdominal and back pain improved 7 days later; at a 3-month follow-up FDG PET-CT scan, the patient achieved partial remission, with an MTV of 14.1 cm^3 and a TLG of 59.1.

In another example, patient 5 was a 33-year-old female with DLBCL involving the anterior mediastinum, left

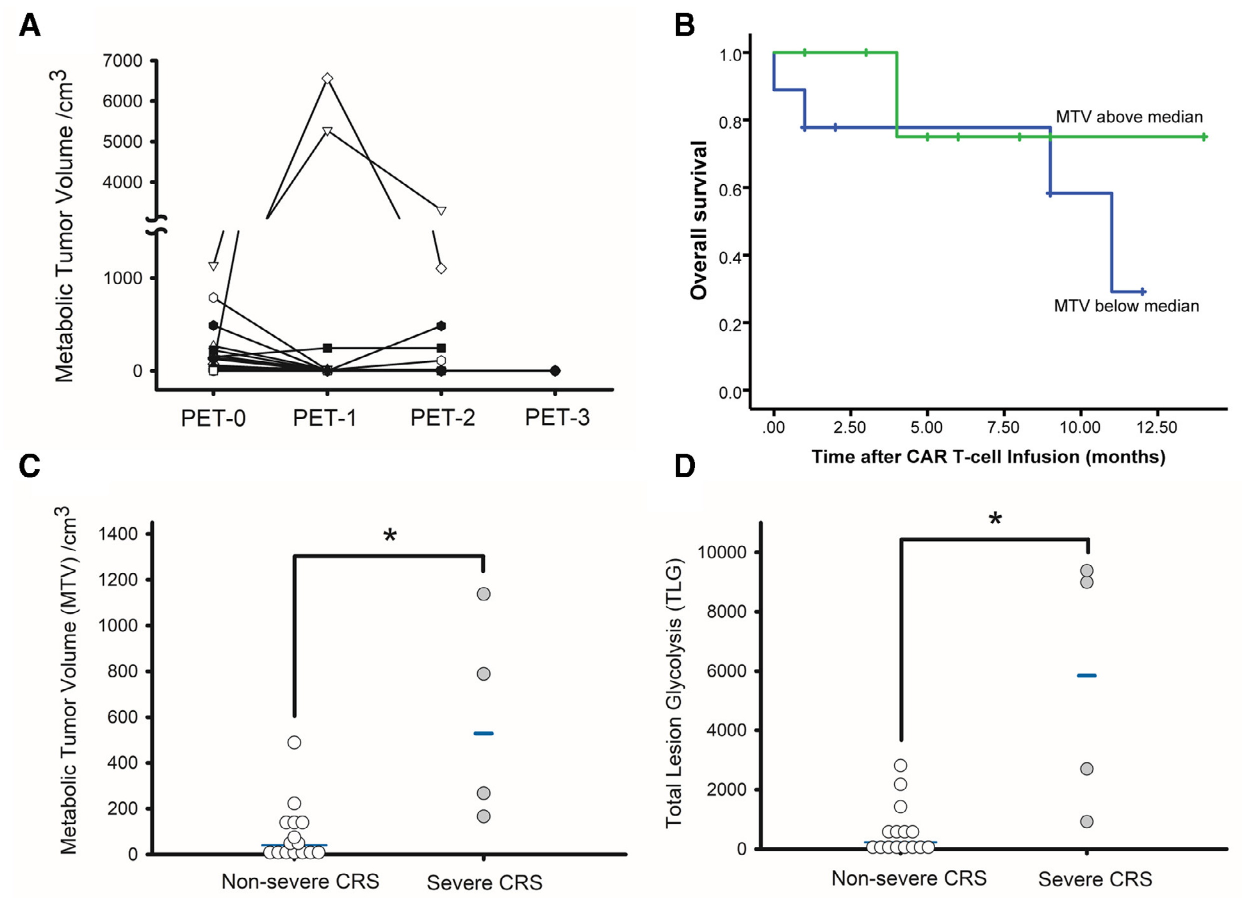

Figure 1. Clinical outcomes and adverse effects of CAR-T cell therapy in patients with NHL. (A) Changes in MTV in 19 patients before (PET-0), 1 month after (PET-1), 2 months after (PET-2), and 3 months after (PET-3) CAR-T cell therapy. (B) No significant difference in OS was observed between patients with baseline MTV above the median and patients with baseline MTV below the median. (C) The median MTV was significantly lower in patients with mild or moderate CRS (grade <3) compared with patients with severe CRS (grade ≥ 3) (49.3 cm^3 versus 1137.7 cm^3; $P = .012$). (D) The median TLG was significantly lower in patients with mild or moderate CRS (grade <3) compared with patients with severe CRS (grade ≥ 3) (379.1 versus 9384; $P = .012$).

pulmonary hilum and multiple subcutaneous nodules (Figure 2A). At 1-1/2 months before CAR-T cell infusion, the anterior mediastinum mass had an MTV of 149.6 cm^3, an SUVmax of 23.5, and a TLG of 1421.1. At 5 days after the infusion, the patient developed dyspnea and facial swelling with distension of the veins in the neck and on the chest wall. Superior vena cava (SVC) syndrome was suspected. A repeat PET-CT performed 1 day later showed an enlarged anterior mediastinum mass extending to the right pulmonary hilum with compression of the SVC, right bronchus, and pulmonary tissues (Figure 2B). The MTV was 298.1 cm^3, SUVmax was 21.8, and TLG was 5316.8. The symptoms resolved within 1 week, and a repeat PET-CT scan 1 month later showed an MTV of 0.76 cm^3.

In another case, patient 12 had a DLBCL involving the right cervical lymph node chain. Four days after the CAR-T cell infusion, the patient developed moderate difficulty breathing with concurrent CRS. An enlarged tumor mass with compression of the main bronchi was confirmed by ultrasound compared with a previous ultrasound performed 5 days earlier. The symptoms improved 3 days later with the resolution of fever. This patient also achieved partial remission.

The median MTV was 267.2 cm^3 (95% CI, 149.6 to 789.1 cm^3) in patients experiencing pseudoprogression, compared with 49.3 cm^3 (95% CI, .02 to 1137.7 cm^3) in responding patients without clinically significant pseudoprogression (P = .09). The median TLG was 2698.7 (95% CI, 1421.2 to 8990.3) in patients who experienced pseudoprogression and 394.2 (95% CI, .03 to 9348.0) in responding patients without pseudoprogression ($P = .07$).

Along with local compression from pseudoprogression, we also observed cases of local immune activation leading to organ damage. Patient 7 has been reported previously [4]. In brief, lymphoma was discovered in the anterior mediastinum, left chest wall, both breasts, and pleura. Four days after CAR-T cell infusion, the patient exhibited shortness of breath with large bilateral pleural effusions. Thoracentesis confirmed infiltration of CAR-T cells into the pleural cavity with elevated cytokines consistent with pleural cavity CRS. Patient 10 was a 35-year-old male with DLBCL involving the right neck, right clavicle, right upper extremity, and myocardium (Figure 3A). The MTV of the myocardium was 28.9 cm^3, with an SUVmax of 8.36 and a TLG of 114.4. Six days after CAR-T cell infusion, the patient complained of worsening shortness of breath. Ultrasound showed pericardial effusion with a depth of 16 mm behind the left ventricular (LV) wall. The patient also developed persistent sinus tachycardia of 120 to 150 bpm with an elevated troponin level. The LV ejection fraction (LVEF) was initially 63% at the time of CAR-T cell infusion but dropped to 52% 9 days later. The pericardial effusion continued to worsen in the subsequent few days (Figure 3B). A repeat FDG PET-CT scan performed 2 weeks after CAR-T cell infusion showed remission of the previous myocardial lesions. However,

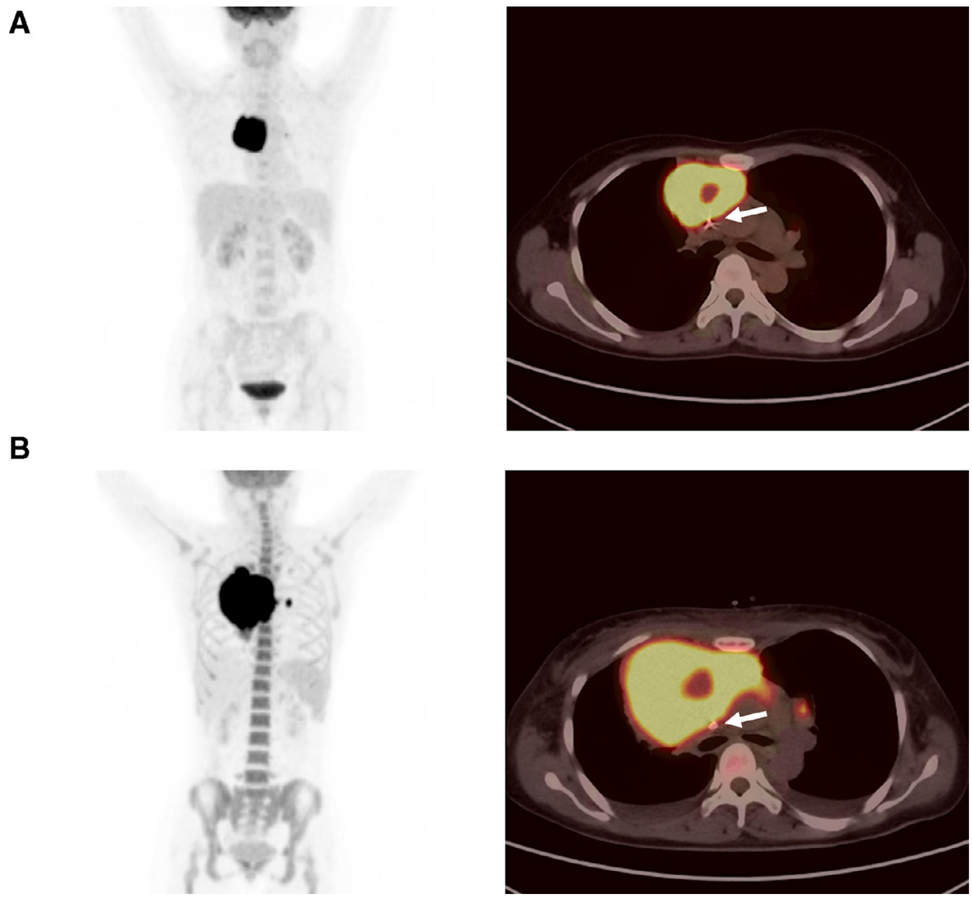

Figure 2. Pseudoprogression of anterior mediastinum lymphoma after CAR-T cell infusion led to SVC syndrome in patient 5. (A) A large mediastinum lymphoma (MTV, 149.6 cm^3; TLG, 1421.1) was detected before CAR-T cell infusion (left). The mass was located at the anterior mediastinum adjacent to the SVC (white arrow, right). (B) Five days after CAR T-cell infusion, the patient developed dyspnea, facial swelling, and distension of the veins in the neck and on the chest wall. A repeat FDG PET-CT scan revealed an enlarged lymphoma (MTV, 298.1 cm^3; TLG, 5316.8) (left), with compression of the SVC (white arrow, right).

diffusely increased FDG uptake in the myocardium was observed, indicating myocarditis (Figure 3C). Finally, pericardial effusion and LVEF gradually improved by 2 weeks after CAR-T cell infusion, although sinus tachycardia persisted until the last follow-up. An FDG PET-CT scan performed 4 weeks after the infusion showed decreased metabolic activity of the myocardium, with less pericardial effusion (Figure 3D).

DISCUSSION

In this study, we have demonstrated the role of FDG PET-CT in predicting the adverse effects and clinical outcomes in patients with NHL treated with CD19-targeting CAR-T cell therapy. MTV, a computer-assisted measurement of total body tumor volume, is considered a better prognostic factor than SUV in solid tumors [17]. TLG, which equals MTV multiplied by average SUV per lesion, indicates the total body tumor metabolic activity, and is considered a more accurate measure of disease burden than SUVmax [18]. Using these 2 parameters, we identified the baseline and post-CAR T-cell therapy disease burden in 19 patients with NHL.

For CAR-T cell therapy in patients with ALL, baseline disease burden has been identified as the key predictor of adverse effects and prognosis. The quantification of NHL disease burden is more difficult, however, because it requires the use of FDG PET-CT. Furthermore, because the tumor microenvironment has s a stronger role in NHL than in ALL, the tumor burden measured by PET-CT might not represent the actual amount of tumor accessible to CAR-T cells [19]. Therefore, the relationship between NHL disease burden and treatment outcomes remains unclear. At the 2018 American Society of Clinical Oncology meeting, Gauthier et al. [20] also showed that for relapsed/refractory DLBCL, increased tumor burden, measured by the sum of the products of the diameters, was adversely associated with progression-free survival and OS. In our study of NHL, we failed to find any effect of baseline MTV/TLG on CR rate or OS. Such a discrepancy might be related to the small patient population in our cohort, which made the study underpowered to identify small differences.

In terms of adverse effects, we found that higher disease burden was associated with more severe CRS. Recent studies have identified CRS as resulting from an interplay among tumor cells, CAR-T cells, and monocytes [13,14]. When CAR-T cells and tumor cells are engaged, CAR-T cells are activated to recruit monocytes; the latter can secrete key CRS cytokines and cause symptoms of CRS. With a greater disease burden, more CAR-T cells and monocytes are activated, leading to more severe CRS. Although previous studies have implied a correlation between disease burden and CRS in NHL [1], we are the first to quantitatively confirm the relationship with measurements of MTV and TLG.

The use of FDG PET-CT also allowed us to identify local side effects. We found rapid lymphoma enlargement leading to local compression in 3 patients. It is important to distinguish pseudoprogression from hyperprogression, which is defined as a rapid increase in tumor size (usually more than twofold) around 1 month after the initiation of immunotherapy [21].

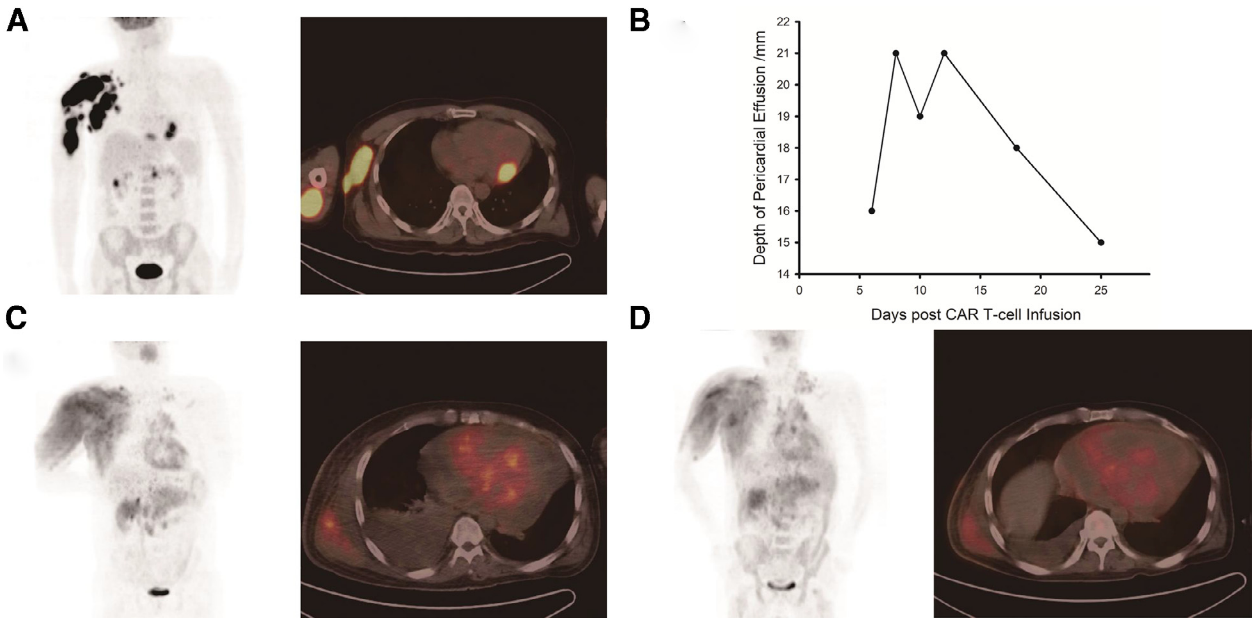

Figure 3. Myocarditis after CAR-T cell therapy in patient 10 with previous myocardium lymphoma. (A) Before CAR-T cell therapy, DLBCL involving the right neck, right clavicle, right upper extremity, and myocardium was observed. (B) Six days after CAR- T cell infusion, ultrasound revealed pericardial effusion. The effusion continued to worsen over the following days but improved after 2 weeks. (C) Repeat PET-CT scan 2 weeks after the infusion showed a decreased tumor burden in the right upper extremity and myocardium but with new lesions in the pelvis (left). Diffusely increased FDG uptake of the myocardium was noticed, indicating myocarditis (right). (D) Four weeks after the infusion, the metabolic activity of the myocardium decreased, and pericardial effusion diminished (right).

We observed hyperprogression in 2 patients (Figure 1A); however, patients 4, 5, and 12 most likely had pseudoprogression. FDG PET-CT clearly revealed tumor enlargement around 1 week after CAR-T cell infusion (Figure 2). We suspected that the increased metabolic activity was most likely secondary to immune cell infiltration, given the unlikelihood of lymphoma doubling in size in such a short period, and all 3 patients exhibited rapid regression after initial enlargement. Of note, however, we did not obtain tissue samples to confirm pseudoprogression, and it remains possible that the enlargement could be related to rapid lymphoma growth.

Of note, the pseudoprogression observed with CAR-T cell therapy was more rapid and significant compared with that with checkpoint inhibitors, which could be secondary to the different malignancy types treated with each therapy but also may reflect a greater efficacy of CAR-T cell therapy. However, such enlargement can cause local compression, with life-threatening consequences. Further studies are needed to identify patients who might experience pseudoprogression, and special attention should be given to the potential for local compression in these patients. CAR-T cell infiltration of tumors also can cause local immune activation, leading to organ damage. Therefore, it is important that PET-CT be used to identify all involved sites in a patient, and precautions should be taken to prevent local organ damage following treatment.

In conclusion, we have shown that the baseline NHL tumor burden as assessed by FDG PET-CT is a useful predictor of adverse effects. A greater baseline tumor burden is significantly associated with more severe CRS, and the relationship between tumor burden and treatment outcomes warrants further exploration.

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