Early evaluation of CAR-T cell therapy response in R/R DLBCL patients using ^{18}F-FDG PET/CT

Kazuhiro Kitajima[1] MD,
Hiroyuki Yokoyama[1] MD,
Reona Wada[1] MD,
Yukihisa Tamaki[2] MD,
Kyoko Yoshihara[3] MD,
Katsuji Kaida[3] MD,
Satoshi Yoshihara[3] MD,
Koichiro Yamakado[1] MD

1.Department of Radiology, Hyogo Medical University, Hyogo, Japan
2. Department of Radiology Shimane University, Faculty of Medicine, Shimane, Japan
3. Department of Respiratory Medicine and Hematology, Hyogo Medical University, Hyogo, Japan

Keywords: Malignant lymphoma - CAR-T - Immunotherapy - Treatment response - ^{18}F-FDG - PET/CT

Corresponding author:
Kazuhiro Kitajima MD, Department of Radiology, Hyogo Medical University, Nishinomiya, Hyogo, Japan, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501 Japan
Phone: +81-798-45-6883,
Fax: +81-798-45-6262
kazu10041976@yahoo.co.jp

Received:
16 February 2024
Accepted revised:
1 March 2024

Abstract

Objective: CD19-targeted chimeric antigen receptor T (CAR-T) cell therapy provides a durable response in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). The role of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) for early evaluation of responsein patients with that immunotherapy was evaluated. **Subjects and Methods:** Three separate ^{18}F-FDG PET/CT examinations of 53 patients (29 males, 24 females; median 62 years old) with R/R DLBCL were conducted; before bridging therapy [time of decision (TD)], before CAR-T (tisagenlecleucel, n=37; lisocabtagenemaraleucel, n=16) infusion [time of CAR-T infusion (IT)], and one month (M1) after CAR-T infusion. Response was evaluated based on the Deauville 5-point scale and Lugano criteria. **Results:** Among 21 patients (39.6%) with complete metabolic response (CMR) at IT-PET, 20 were able to continue CMR, while one showed progression at M1-PET. Among 32 patients (60.4%) with non-CMR at IT-PET, 12, 8, 4, and 8 showed CMR, partial metabolic response (PMR), (non-metabolic response (NMR), and progressive metabolic disease (PMD), respectively, at M1-PET as compared with IT-PET. Evaluations of M1-PET as compared with baseline TD-PET indicated 32, 7, 5, and 9 patients with CMR, PMR, NMR, and PMD, respectively. After a median 10.1 months, 26 patients showed progression and 13 had died from DLBCL. The 32 who achieved CMR showed significantly longer progression-free (P<0.0001) and overall survival (P<0.0001) periods as compared to the 21 non-CMR patients. **Conclusion:** Fluorine-18-FDG PET/CT findings obtained one month after CAR-T cell therapy showed accuracy for early response evaluation and prediction of progression in patients with R/R DLBCL.

Hell J Nucl Med 2024; 27(1): 8-15 *Epub ahead of print: 18 April 2024* *Published online: 30 April 2024*

Introduction

Overall survival (OS) of patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) who have failed at least two treatment regimens has been estimated to be only 4.4 to 6.3 months [1, 2]. However, those patients had limited treatment options, as the studies were presented prior to recent approval of two commercially available CD19-targeted chimeric antigen receptor T (CAR-T) cell therapy agents; axicabtageneciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) [3-5]. Data obtained in later pivotal trials suggest durable remission in 30% to 40% of patients with R/R DLBCL who undergo CAR-T cell therapy [4, 5].

Adequate assessment of systemic treatment response is crucial for effective cancer treatment management, which includes effective means to monitor responsiveness of the tumor to systemic therapy, while that is also extremely important for moderation of the high risk of mortality as well as toxic effects known to be associated with available systemic therapeutic regimens. Early identification of a poor responder is important, as such patients will require aggressive treatment, and use of ineffective or toxic systemic therapy agents should be avoided.

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) plays a key role in management of patients with DLBCL, with the results shown to be effective for predicting outcome at specific time points in an earlier course of the disease [6-9]. Several recently presented studies reported the utility of baseline and follow-up ^{18}F-FDG PET/CT results for assessing therapeutic response in cases of R/R DLBCL treated with CAR-T cell therapy, as well as prognosis prediction [10-14]. However, to the best of our knowledge, only three examined the performance of ^{18}F-FDG PET/CT for early treatment response within one month after start of CAR-T cell therapy [10-12]. Therefore, the true usefulness of ^{18}F-FDG PET/CT for evaluation of early treatment response in affected patients has not been clarified.

The present study was performed to investigate the usefulness of ^{18}F-FDG PET/CT fin-

dings for evaluating early treatment response in patients with R/R DLBCL, who underwent such an examination before and again one month after CAR-T cell therapy. Furthermore, the usefulness of those findings for prediction of prognosis was analyzed.

Subjects and Methods

Patients

This retrospective study was approved by the ethics committee of our institution. The need for informed consent was waived. Patients that met the following inclusion criteria were enrolled: 1) over 18 years old; 2) treated with CAR-T cell therapy (tisagenlecleucel or lisocabtagenemaraleucel) for R/R DLBCL at our institution between January 2020 and June 2023; and 3) underwent three ^{18}F-FDG PET/CT examinations for assessment of lymphoma lesions, including before bridging therapy (time of decision: TD), before undergoing CAR-T infusion (time of CAR-T infusion: IT), and one month after CAR-T infusion (M1). The median interval between TD-PET scan and bridging therapy initiation was 0.7 months (range 0.1-1.8 months), between TD and IT PET studies was 2.0 months (range 1.3-2.9 months), and between IT-PET examination and CAR-T transfusion was 0.3 months (range 0.03-1.1 months). After receiving CAR-T cell therapy, follow-up ^{18}F-FDG PET/CT examinations were performed one month later, then again every three months for the first year and every six months for the second year, and annually thereafter.

^{18}F-FDG PET/CT examinations

All ^{18}F-FDG-PET/CT examinations were performed using an Ingenuity TF (Philips Medical Systems, Eindhoven, The Netherlands) or Discovery IQ (GE Healthcare, Waukesha, WI, USA) scanner, with the same device used for the three scans in individual patients. They were instructed to fast for at least five hours before the examination, then blood glucose was measured immediately prior to ^{18}F-FDG injection at 3.7 MBq/kg of body weight, with all in the present cohort showing a level less than 160mg/dL. Static emission images were obtained approximately 60 minutes after the injection. For attenuation correction and anatomic localization, helical CT scan images from the top of the head to bottom of the feet were obtained using the following parameters: tube voltage, 120kV (all four scanners); effective tube current automA up to 155mA (Ingenuity TF) or 15-390mA (Smart mA: noise index 25) (Discovery IQ); gantry rotation speed, 0.5/second; detector configuration of 64×0.625mm (Ingenuity TF) or 16mm×1.25mm (Discovery IQ); slice thickness, 2 mm; and transverse field of view of 600mm (Ingenuity TF) or 700 mm (Discovery IQ). Immediately after completion of the CT examination, PET imaging was performed from the head to mid-thigh for 90 seconds(Ingenuity TF) or 180 seconds (Discovery IQ) for each bed position, and mid-thigh to tips of the toes for 30 seconds (Ingenuity TF) or 45 seconds (Discovery IQ) for each bed position in three-dimensional mode. The patient was allowed to breathe normally during PET scanning. For the Ingenuity TF, an ordered-subset expectation maximization (OSEM) iterative image reconstruction algorithm (33 subsets, 3 iterations) was used, while Q.Clear reconstruction [block sequential regularized expectation maximization (BSREM)] (β=400) was utilized for the Discovery IQ.

Image interpretation

All ^{18}F-FDG PET/CT images were retrospectively reviewed by two experienced nuclear medicine physicians, one a board-certified nuclear medicine physician with 15 years of experience and the other with five years of experience with oncologic ^{18}F-FDG PET/CT, with neither having knowledge of the other imaging results, nor clinical or progression data, other than those obtained in prior examinations, during and after CAR-T cell therapy for R/R DLBCL. Consensus regarding the findings was obtained by discussion. The visual Deauville 5-point scale in accordance with the Lugano criteria was used for determination of objective response [15]. Two different evaluation methods were utilized to classify patients as showing complete metabolic response (CMR), partial metabolic response (PMR), non-metabolic response (NMR), or progressive metabolic disease (PMD). To determine mediastinal blood pool and liver uptake values for reference settings, a 5-point scale was used. According to the Lugano classification, achievement of CMR was defined as a completely PET negative scan, or a scan with minimal residual uptake that was less than or equal to liver activity (Deauville score $\leq$3). For cases with a Deauville score of 4 or 5, PMR, NMR, or PMD was defined using visual comparison with a previous PET scan. Four representative cases are presented in Figures 1-4.

Statistical analysis

Progression-free survival (PFS) was defined based on time elapsed from the start of CAR-T cell therapy to the date of disease progression or recurrence of R/R DLBCL revealed in radiological and/or clinical examination results, or death from any cause. Patients with no evidence of progressive disease or recurrence were censored on the date of the last follow-up examination. Overall survival was defined as the start of CAR-T cell therapy until death from R/R DLBCL. Patients alive at the final follow-up examination were censored, with 'alive with disease' or 'no evidence of progression' used for the classification. Actuarial survival curves were generated using the Kaplan-Meier method and a log-rank test was employed to examine differences between groups. The SAS software package, version 9.3 (SAS Institute Inc., Cary, NC, USA), was utilized for statistical analyses, with P values <0.05 considered to indicate statistical significance.

Results

Fifty-three patients (29 males, 24 females; median 62 years old, range 21-74 years old) with R/R DLBCL who underwent CAR-T cell therapy (tisagenlecleucel, n=37; lisocabtagenemaraleucel, n=16) were included in the present study.

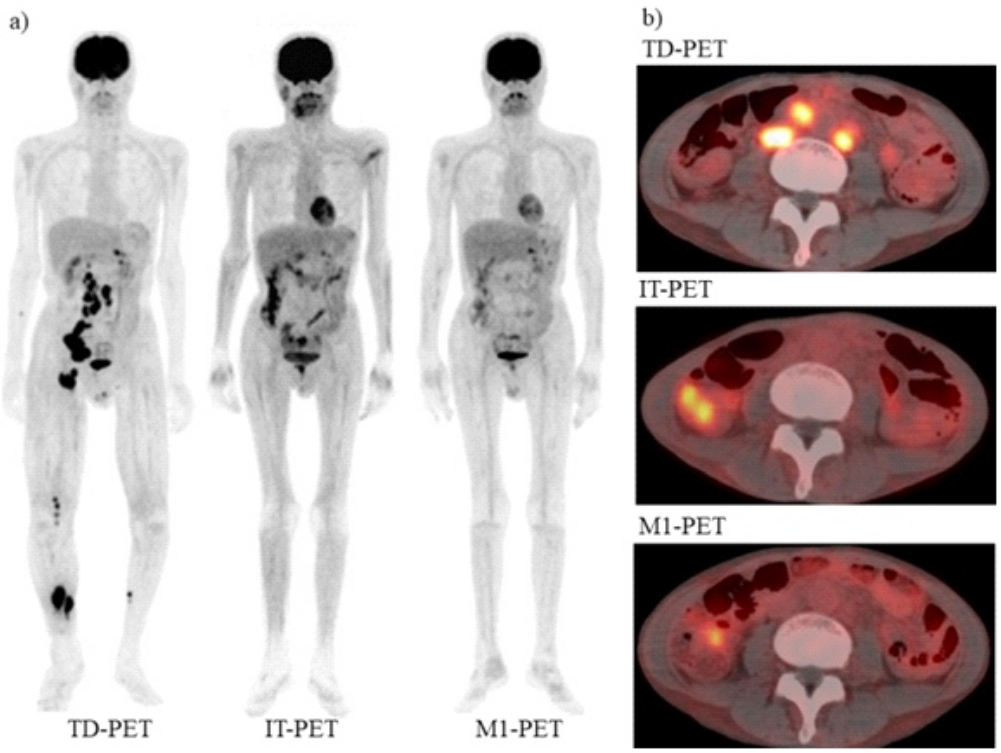

Figure 1. Male, 52 years old, with R/R DLBCL received lisocabtagenemaraleucel. a) Maximum intensity projection (MIP) of baseline TD-PET before bridging therapy showing several areas of intense ^{18}F-FDG uptake in abdominal, pelvic, right inguinal, and bilateral leg regions. IT-PET scanning performed before CAR-T therapy revealed complete resolution of abnormal metabolic activity with an objective response of CMR, while M1-PET performed one month after CAR-T infusion showed continuance of no abnormal uptake, with an objective response of CMR. b) TD-PET image showing multiple swollen para-aortic lymph nodes with intense ^{18}F-FDG uptake. IT-PET findings indicated a decreased number of nodes with vanishing ^{18}F-FDG uptake, while M1-PET showed a continuance of no abnormal uptake.

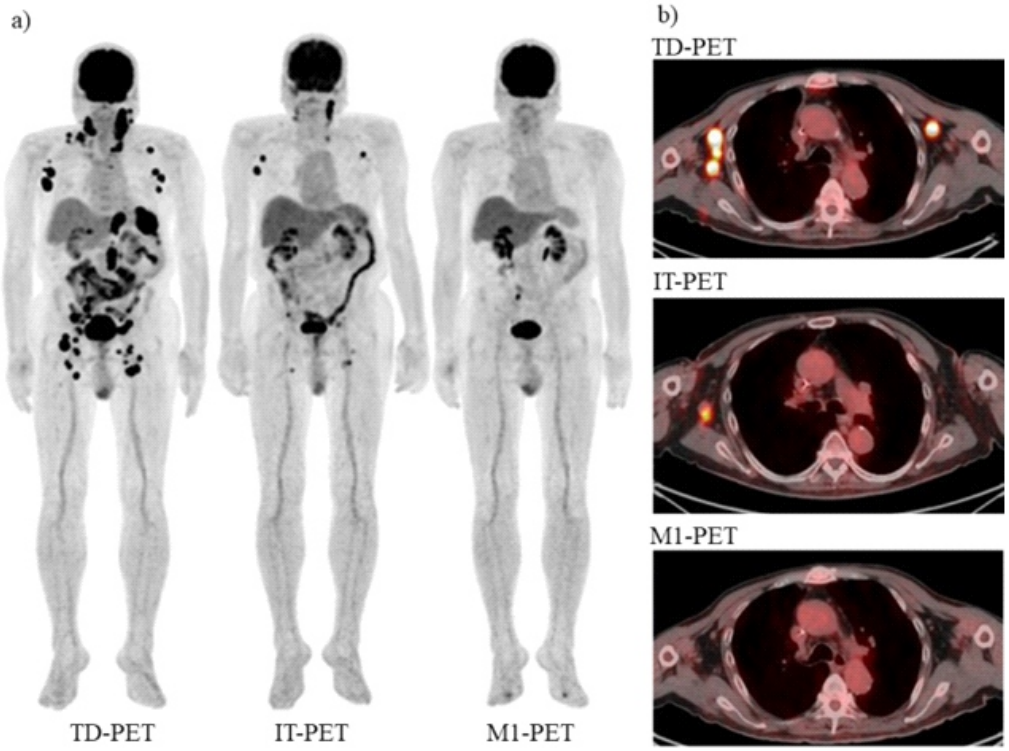

Figure 2. Male, 74 years old, with R/R DLBCL received tisagenlecleucel. a) MIP of baseline TD-PET showing several areas with abnormal ^{18}F-FDG uptake in bilateral neck, bilateral axilla, spleen, abdominal, pelvic, and bilateral inguinal regions. IT-PET showed decreased ^{18}F-FDG activity in same areas with an objective response of PMR, while M1-PET showed complete resolution of abnormal metabolic activity in those areas, with an objective response of CMR. b) TD-PET image showing swollen bilateral axilla lymph nodes with intense ^{18}F-FDG uptake. IT-PET indicated a transient decline in metabolic activity in those nodes, while M1-PET revealed that the lesion was decreased and no abnormal ^{18}F-FDG uptake.

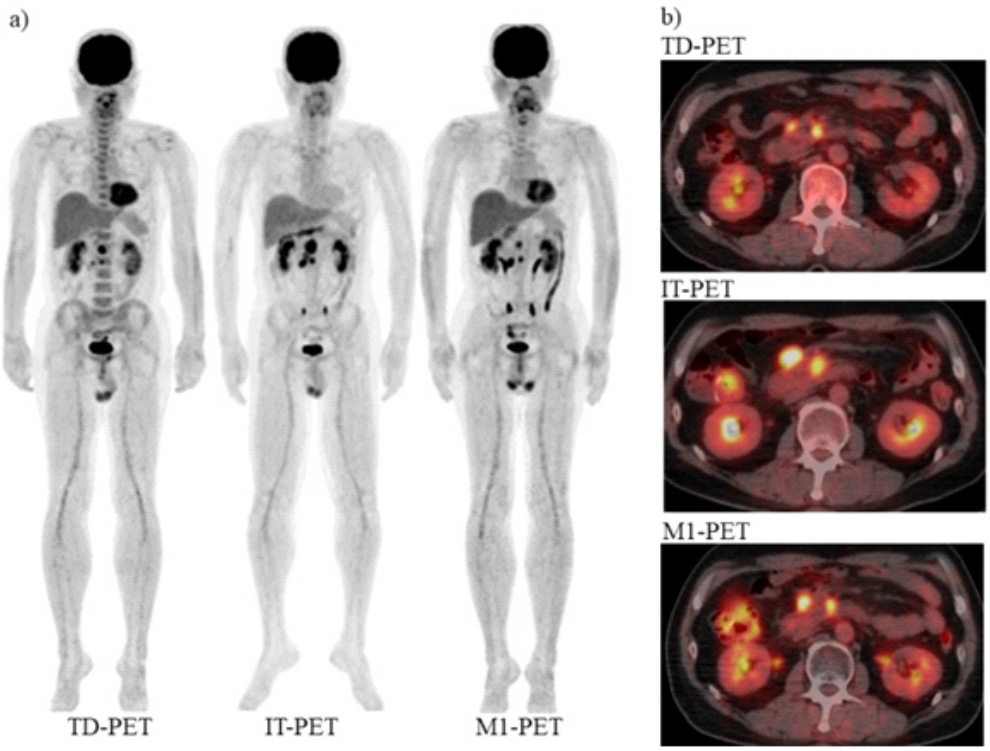

Figure 3. Male, 50 years old, with R/R DLBCL received tisagenlecleucel. a) MIP of baseline TD-PET showing several areas of abnormal ^{18}F-FDG uptake in the abdomen. IT-PET showed increased ^{18}F-FDG activity in those areas with an objective response of PMD. M1-PET showed decreased ^{18}F-FDG activity in those areas with an objective response of PMR, though the level of ^{18}F-FDG uptake was nearly the same in comparison with the baseline TD-PET findings, with an objective response of NMR. b) TD-PET image showing swollen para-aortic lymph nodes with moderate ^{18}F-FDG uptake. IT-PET showed an increase in metabolic activity in that node, while M1-PET revealed that the metabolic activity of the lesion had declined. Evaluations of M1-PET as compared with baseline TD-PET findings indicated no change.

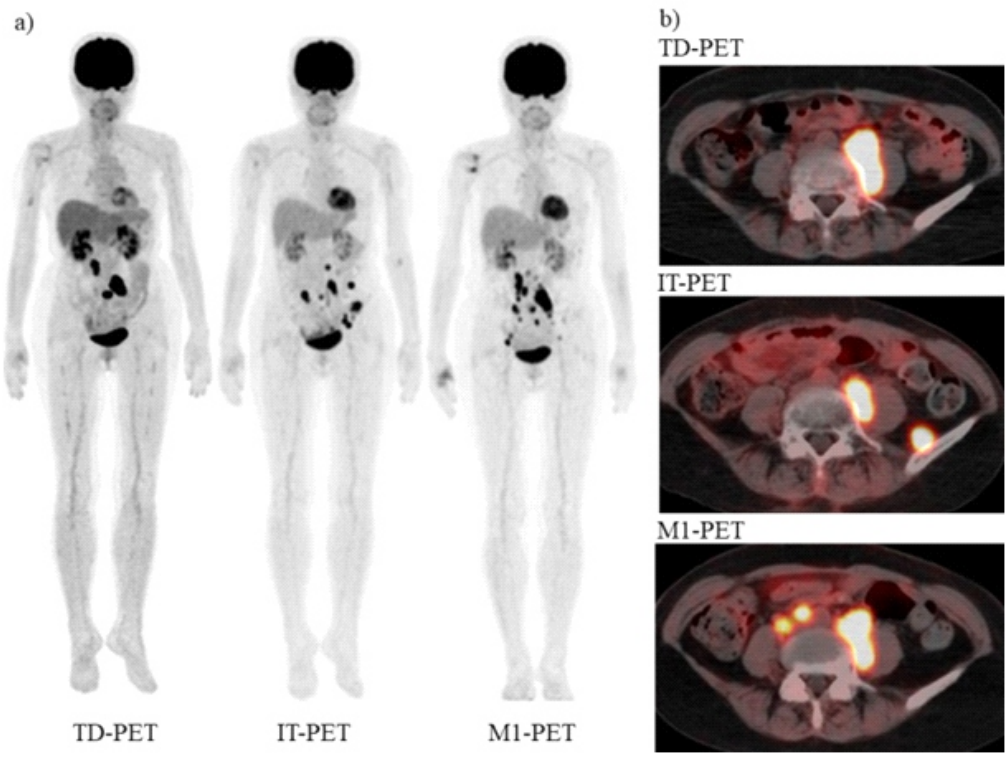

Figure 4. Female, 67 years old, with R/R DLBCL received lisocabtagenemaraleucel. a) MIP of baseline TD-PET showing several areas of abnormal ^{18}F-FDG uptake in the abdominal and pelvic regions. IT-PET showed decreased ^{18}F-FDG activity in the same areas, though new abnormal ^{18}F-FDG uptake in the pelvis was noted, with an objective response of PMD. M1-PET showed increased as well as decreased ^{18}F-FDG activities in those regions, as well as new lesions in the abdominal and pelvis region, with an objective response of PMD. Evaluations of M1-PET as compared with baseline TD-PET finding indicated new lesions, with an objective response of PMD. b) TD-PET image showing swollen pelvic lymph nodes with intense ^{18}F-FDG uptake. IT-PET showed decreased ^{18}F-FDG activity in the same area along with new nodes with intense ^{18}F-FDG uptake. M1-PET showed both increasing and disappearance of ^{18}F-FDG activities in those regions, and new nodal lesions.

Treatment response

Evaluations of IT-PET as compared with baseline TD-PET findings revealed CMR, PMR, NMR, and PMD in 21 (39.6%), 14 (26.4%), 9 (17.0%), and 9 (17.0%) patients, respectively. Of the 21 patients who achieved CMR at IT-PET, 20 (95.2%) could continue CMR at M1-PET, while one patient (4.8%) showed progression (PMD) at M1-PET (Table 1). Among 32 patients (60.4%) with non-CMR at IT-PET, 12 patients (PMR: 8 patients, NMR: 1, and PMD: 3) could achieved CMR, 8 patients (PMR: 2 patients, NMR: 3, and PMD: 3) developed PMR, 4 patients (NMR: 4) demonstrated NMR, and 8 patients (PMR: 4 patients, NMR: 1, and PMD: 3) showed PMD at M1-PET, in comparison with IT-PET.

Furthermore, evaluations of M1-PET findings as compared with the baseline showed TD-PET, CMR, PMR, NMR, and PMD in 32 (60.4%), 7 (13.2%), 5 (9.4%), and 9 (17.0%) patients, respectively.

Survival analysis

Progression or recurrence of R/R DLBCL was noted in 26 (49.1%) of the 53 patients, with a median period of 5.8 months (1.0-40.4 months). As compared with baseline TD-PET, nine (28.1%) of the 32 with CMR at M1-PET/CT and 17 (81.0%) of 21 non-CMR patients (PMR/NMR/PMD) showed progression or recurrence. Those who achieved CMR had a significantly longer PFS as compared to the non-CMR group (P<0.0001) (Figure 5a). Furthermore, 12 (30.8%) of 39 patients with metabolic response (CMR/PMR) shown at M1-PET/CT as compared with baseline TD-PET developed progression or recurrence, while all 14 (100%) of the non-responders (NMR/PMD) showed such development. Patients considered to be metabolic responders (CMR/PMR) had a significantly longer PFS as compared to non-responders (NMR/PMD) (P<0.0001) (Figure 5b). Moreover, 17 (38.6%) of 44 with no progression (CMR/PMR/NMR) at M1-PET/CT as compared with baseline TD-PET, as well as all nine (100%) with PMD showed progression or recurrence. Patients with no progression (CMR/PMR/NMR) had a significantly longer PFS as compared to the PMD group (P<0.0001) (Figure 5c).

Death from R/R DLBCL occurred in 26 (49.1%) of the 53 patients, with a median period of 10.1 months (1.5-40.5 months). Two (6.3%) of 32 with CMR shown in M1-PET/CT findings as compared with baseline TD-PET died, as compared to 11(52.4%) of the 21 non-CMR patients (PMR/NMR/PMD) with mortality. Patients who achieved CMR had a significantly longer OS as compared to the non-CMR group (P< 0.0001) (Figure 6a). Furthermore three (7.7%) of 39 patients who showed metabolic response (CMR/PMR) in M1-PET/CT findings as compared with baseline TD-PET died, whereas 10 (71.4%) of 14 non-responders (NMR/PMD) were mortality cases. Patients with metabolic response (CMR/PMR) had a significantly longer OS as compared to the non-responders (NMR/PMD) (P<0.0001) (Figure 6b). Finally, seven (15.9%) of

Table 1. *Treatment response evaluation.*

TD-PET before bridging therapy	IT-PET before CAR-T	M1-PET
(time of decision: TD)	(time of CAR-T infusion: IT)	(1 month after CAR-T infusion)
20 pts (37.7%)	CMR	CMR
12 pts (22.6%)	non-CMR (PMR:8/NMR:1/PMD:3)	CMR
1 pt (1.9%)	CMR	non-CMR (PMD)
8 pts (15.1%)	non-CMR (PMR:2/NMR:3/PMD:3)	PMR
4 pts (7.5%)	non-CMR (NMR:4)	NMR
8 pts (15.1%)	non-CMR (PMR:4/NMR:1/PMD:3)	PMD
32 pts (60.4%)	not evaluated	CMR
7 pts (13.2%)	not evaluated	PMR
5 pts (9.4%)	not evaluated	NMR
9 pts (17.0%)	not evaluated	PMD

pts: patients, CMR: complete metabolic response, PMR: partial metabolic response, NMR: non-metabolic response, PMD: progressive metabolic response

44 patients with no progression (CMR/PMR/SMD) at M1-PET/CT as compared with baseline TD-PET and six (66.7%) of nine with PMD died. Patients with no progression (CMR/PMR/NMR) had a significantly longer OS as compared to the PMD group (P=0.0011) (Figure 6c).

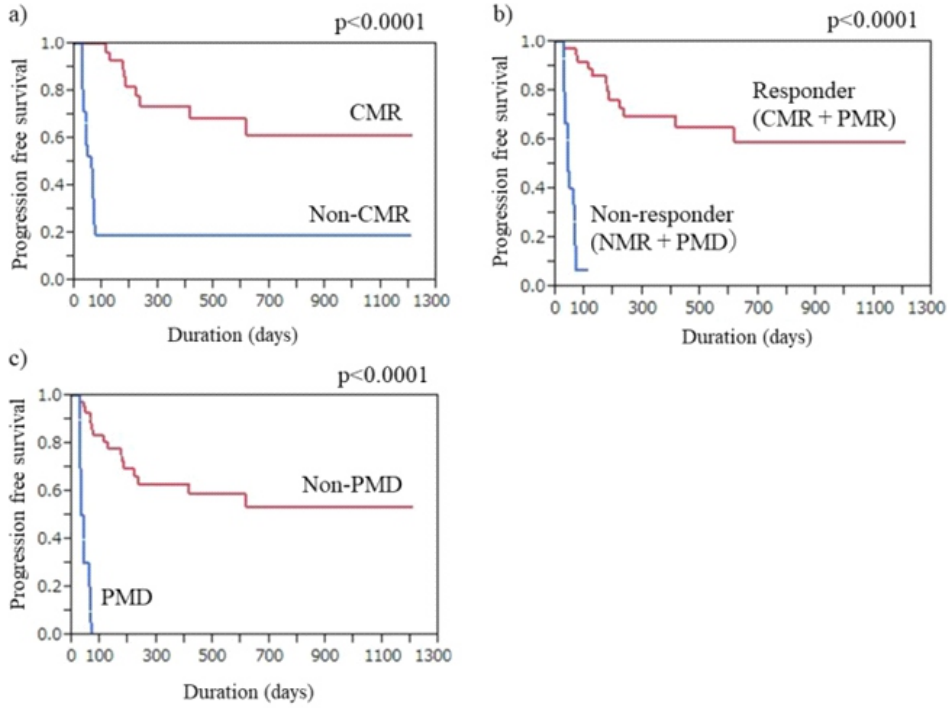

Figure 5. Progression-free survival (PFS) of R/R DLBCL patients who received CAR-T immunotherapy.a) Kaplan-Meier curves showing that 32 patients who achieved CMR had significantly longer PFS than 21 with non-CMR (PMR/NMR/PMD) (P<0.0001). b) Kaplan-Meier curves showing that 39 patients classified as metabolic responders (CMR/PMR) had significantly longer PFS than 14 non-responders (NMR/PMD) (P<0.0001). c) Kaplan-Meier curves showing that 44 patients with no progression (CMR/PMR/NMR) had significantly longer PFS than nine with PMD (P<0.0001).

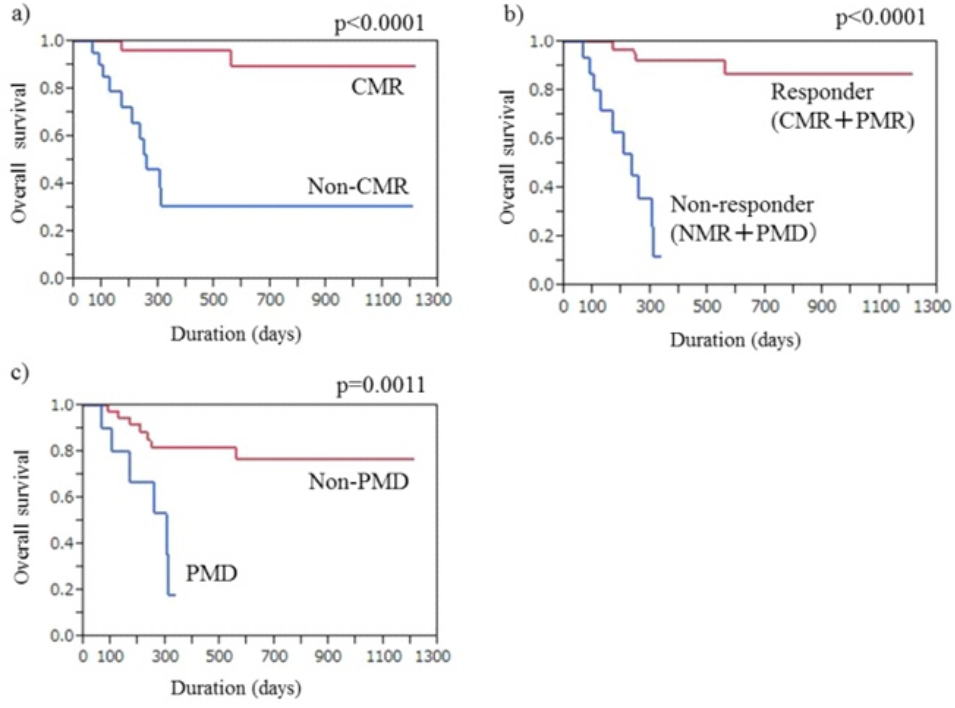

Figure 6. Overall survival (OS) of R/R DLBCL patients who received CAR-T immunotherapy. a) Kaplan-Meier curves showing that 32 patients who achieved CMR had significantly longer OS than 21 with non-CMR (PMR/NMR/PMD) (P<0.0001). b) Kaplan-Meier curves showing that 39 patients classified as metabolic responders (CMR/PMR) had significantly longer OS than 14 non-responders (NMR/PMD) (P<0.0001). c) Kaplan-Meier curves showing that 44 patients with no progression (CMR/PMR/NMR) had significantly longer OS than nine with PMD (P=0.0011).

Discussion

Introduction of CAR-T cell therapy for R/R DLBCL patients has provided a promising approach. Nevertheless, this novel technology requires a developed clinical infrastructure and involves complicated logistics, while it may also be associated with severe toxicity, with variable therapeutic responses noted. Once CAR-T infusion has been performed, failure should be identified as early as possible to enable a change in treatment. Serial ^{18}F-FDG PET/CT scanning examinations have been included in the imaging algorithm of patients with DLBCL, including a baseline scan performed at diagnosis, and scans during and after first-line treatment, as well as when recurrence is suspected [15]. When PET/CT scan findings identify viable R/R DLBCL and the clinician determines that CAR-T is indicated, the next study is referred to as a TD-PET scan [12]. An IT-PET scan is usually performed immediately prior to CAR-T infusion, with most patients receiving bridging therapy between TD-PET and IT-PET scans. For monitoring response to CAR-T cell therapy, PET/CT is usually performed early and continued later.

Monitoring patient response to CAR-T cell therapy is essential in order to identify CAR-T failure as early as possible, as early identification of a poor responder is important for beginning aggressive treatment and also because ineffective or toxic systemic therapy agents should be avoided in these cases. Of great importance is a practical tool that can correctly differentiate between responders, with longer predicted OS, and non-responders, with shorter predicted OS. Several groups have reported introduction of a scheduled scan performed a tone month after CAR-T infusion, referred to as M1-PET, for early assessment of treatment response [10-12]. Based on their reports of the usefulness of M1-PET for assessing response and predicting prognosis, that was applied in this study.

In the present series of cases, there was no flare-up phenomenon orpseudoprogression observed in M1-PET findings. Pseudoprogression after initiating immunotherapy corresponds to intense inflammatory activity secondary to immune-cell infiltration in target lesions, with that generally occurring fromfour to 12 weeks after checkpoint inhibitor initiation in solid cancer cases [16], while that manifests clinically within the first several days after CAR-T infusion in malignant lymphoma cases [17, 18]. Awareness of the unique time frame of possible pseudoprogression after CAR-T infusion is critical for clinicians and interpreting physicians to correctly schedule ^{18}F-FDG PET/CT examinations, as well as interpret the results. Additionally, several recent studies have demonstrated that establishment of pre-therapy ^{18}F-FDG PET/CT parameters before bridging therapy or CAR-T immunotherapy, such as highest standardized uptake value or total metabolic tumor volume, is associated with prognosis and may assist in patient selection [10,12-14].

The present study has some limitations, including its retrospective design. Furthermore, the sample size is relatively small, which limits generalization and could possibly introduce statistical errors. In addition, the follow-up period after CAR-T cell therapy was insufficient. A larger prospective study with a longer follow-up period will be needed to validate the present results.

In conclusion, ^{18}F-FDG PET/CT findings obtained one month after performing CAR-T cell therapy in patients with R/R DLBCL showed accuracy for early response evaluation and prediction of progression. Early identification of poor responders is important, as those patients will require aggressive treatment, and use of ineffective or toxic systemic therapy agents should be avoided.

Funding Source
This study was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 22K07757).

The authors declare that they have no conflicts of interest

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