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Outcome Prediction in Patients With Large B-cell Lymphoma Undergoing Chimeric Antigen Receptor T-cell Therapy

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ABSTRACT

The introduction of chimeric antigen receptor (CAR) T-cell therapy has led to a fundamental shift in the management of relapsed and refractory large B-cell lymphoma. However, our understanding of risk factors associated with non-response is still insufficient and the search for predictive biomarkers continues. Some parameters measurable on ^{18}F-fluorodeoxyglucose positron emission tomography (PET) may be of additional value in this context. A total of 47 individuals from three German university centers who underwent re-staging with PET prior to CAR T-cell therapy were enrolled into the present study. After multivariable analysis considering tumor characteristics and patient factors that might affect progression-free survival (PFS), we investigated whether metabolic tumor volume (MTV) or maximum standardized uptake value (SUV_{max}) further improve risk stratification. Their most suitable cut-offs were determined by Cox and logistic regression. Forward selection identified extra-nodal disease as the most predictive factor of those routinely available, and we found it to be associated with significantly inferior overall survival after CAR T-cell treatment ($P = 0.012$). Furthermore, patients with MTV and SUV_{max} higher than the optimal threshold of 11 mL and 16.7, respectively, experienced shorter PFS ($P = 0.016$ and 0.002, respectively). Hence, these risk factors might be useful for selection of individuals likely to benefit from CAR T-cell therapy and their management.

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INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy can induce long-term remission in a considerable proportion of patients with relapsed or refractory large B-cell lymphoma.[1–3] However, potential biomarkers for identifying individuals most likely to benefit from this novel treatment are still under investigation. In the phase II JULIET trial, elevated lactate dehydrogenase (LDH) before infusion of tisagenlecleucel was associated with significantly shorter progression-free (PFS) and overall survival (OS).[4] Moreover, a study by Locke et al[5] showed that pretreatment tumor burden estimated on computed tomography (CT) as defined in the Cheson criteria, LDH, and interleukin-6 correlate with the probability of durable response to axicabtagene ciloleucel.

Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) has become an essential diagnostic modality for the staging and response assessment of large B-cell lymphoma.[6–9] It is highly accurate in detecting both nodal and extra-nodal (EN) sites of disease.[10,11] Some recently introduced PET-derived biomarkers might further improve risk stratification and have been shown to provide significant prognostic value for individuals undergoing chemoimmunotherapy.[12–15] There is only limited data available on the role of novel parameters such as metabolic tumor volume (MTV) in identifying patients best suited for CAR T-cell treatment.[16–18]

Therapy decisions should ideally be based on both tumor characteristics and individual patient factors. Yet, there is no established predictive model for the specific context of CAR

T-cell treatment. We therefore set out to examine potential risk factors taking PET metrics into account.

MATERIALS AND METHODS

Study cohort

After approval by the institutional ethics committee, patients treated through January 31, 2021, were enrolled in our study based on the following criteria:

(1) relapsed or refractory, biopsy-proven large B-cell lymphoma;
(2) PET scan performed within 30 days of tisagenlecleucel or axicabtagene ciloleucel infusion;
(3) no cytoreductive treatment between imaging and final product administration besides fludarabine and cyclophosphamide or local radiotherapy.

The three participating German university centers identified a total of 47 individuals suitable for analysis. All of them provided written informed consent before PET examination and CAR T-cell therapy.

Quantitative PET evaluation

MTV measurements were performed semi-automatically without lower lesion volume limit by two expert readers using the ACCURATE tool (PETRA consortium, Amsterdam, The Netherlands) and syngo.via (Siemens Healthcare GmbH, Erlangen, Germany) based on a standardized uptake value (SUV) threshold of 4.0. In lymphoma tissue surrounded by areas of high physiological FDG uptake, particularly intracerebral lesions, manual correction was needed to avoid overestimating the tumor volume. Moreover, we documented the maximum SUV (SUV_{max}) as an additional metabolic parameter.

Definition of predictive factors and statistical analysis

Patient outcomes following CAR T-cell treatment were measured in our study by PFS as well as OS, using the Kaplan–Meier method for assessment of one-year survival and log-rank test to compare risk groups. Median follow-up duration was calculated with a reverse Kaplan–Meier estimator.

We identified the most predictive model for PFS in multivariable analysis based on forward selection through Akaike's information criterion (AIC) using Cox and logistic regression. Here, tumor stage, the presence of more than one EN disease site, LDH elevation, patient age, Eastern Cooperative Oncology Group score, treatment lines, C-reactive protein (CRP) values, and response after bridging therapy were considered as factors that might affect the outcome. The optimal threshold of CRP, MTV, and SUV_{max} for PFS was determined by Cox as well as logistic regression based on AIC and receiver operating characteristic (ROC) analysis with Youden's index, respectively. Our study also examined potential correlations between factors and whether higher metabolic tumor burden represents a risk for the development of cytokine release (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) using Pearson's coefficients.

Baseline data were collected from the electronic medical records and evaluated through descriptive methods. Moreover, we assessed the inter-observer variability in PET volume measurements based on a test set of 24 individuals, using linear regression to ensure that MTVs calculated by the two readers could be pooled. All statistical analysis was conducted with SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Median age at time of treatment was 61 years and 18 individuals were female (38%). The majority had diffuse large B-cell lymphoma (n = 33, 70%), followed by transformed follicular lymphoma (n = 10, 21%), primary mediastinal B-cell lymphoma (n = 2, 4%), and high-grade B-cell lymphoma (n = 2, 4%). Bridging therapy was administered in all enrolled patients and 26 were refractory thereafter (55%). While 43 individuals received tisagenlecleucel (91%), four underwent treatment with axicabtagene ciloleucel (9%). Further baseline characteristics and disease-related information are provided in Table 1.

Outcome prediction using patient and tumor-related factors

Forward selection identified EN disease as the most predictive factor with a hazard ratio (HR) of 1.71 (95% confidence interval [CI] 0.92-3.17). No other patient or tumor characteristic considered was of added value in our analysis set.

After a median follow-up time of 17.03 months, one-year PFS and OS probabilities were 8.0% (95% CI 2.1-30.2%) and 38.6% (95% CI 23.3-63.9%) for the subgroup of individuals who had more than one EN lesion (Figure 1A and B). Patients free of this risk factor achieved a one-year PFS rate of 18.2% (95% CI 7.5-44.1%, $P = 0.083$) and OS probability was significantly superior ($P = 0.012$) with 67.0% (95% CI 49.6-90.5%).

PET measurements and association with survival

The patients included underwent PET scanning a median of 7 days (range 0–29 days) before CAR T-cell administration. Linear regression analysis yielded a slope coefficient and R-squared of 0.91 and 0.98, respectively, for metabolic lymphoma burden indicating comparable values between the two expert readers. Median MTV before CAR T-cell treatment

Table 1

Patient and Disease Characteristics Before CAR T-cell Administration

Age (y)	Median	61
	Range	19–82
Sex	Female	18 (38)
	Male	29 (62)
Lymphoma subtype	Diffuse large B-cell lymphoma	33 (70)
	Transformed follicular lymphoma	10 (21)
	Primary mediastinal B-cell lymphoma	2 (4)
	High-grade B-cell lymphoma	2 (4)
IPI factors	Age >60 y	25 (53)
	Ann Arbor stage III or IV	30 (64)
	More than one EN lesion	25 (53)
	ECOG performance status ≥2	10 (21)
	Elevated LDH	32 (68)
IPI score	1–2	20 (43)
	3–5	27 (57)
Bulky disease[a]	Yes	6 (13)
	No	41 (87)
Treatment lines	Median	3
	Range	2–12
Prior stem-cell transplantation	Autologous	15 (32)
	Allogeneic	1 (2)
Response to bridging therapy	Complete remission	6 (13)
	Partial response	15 (32)
	Stable disease	5 (11)
	Progressive disease	21 (45)

Data are n (%) unless specified otherwise.

[a]Nodal mass with a diameter of ≥7.5 cm in at least one axis.

CAR = chimeric antigen receptor; ECOG = Eastern Cooperative Oncology Group; EN = extra-nodal; IPI = International Prognostic Index; LDH = lactate dehydrogenase.

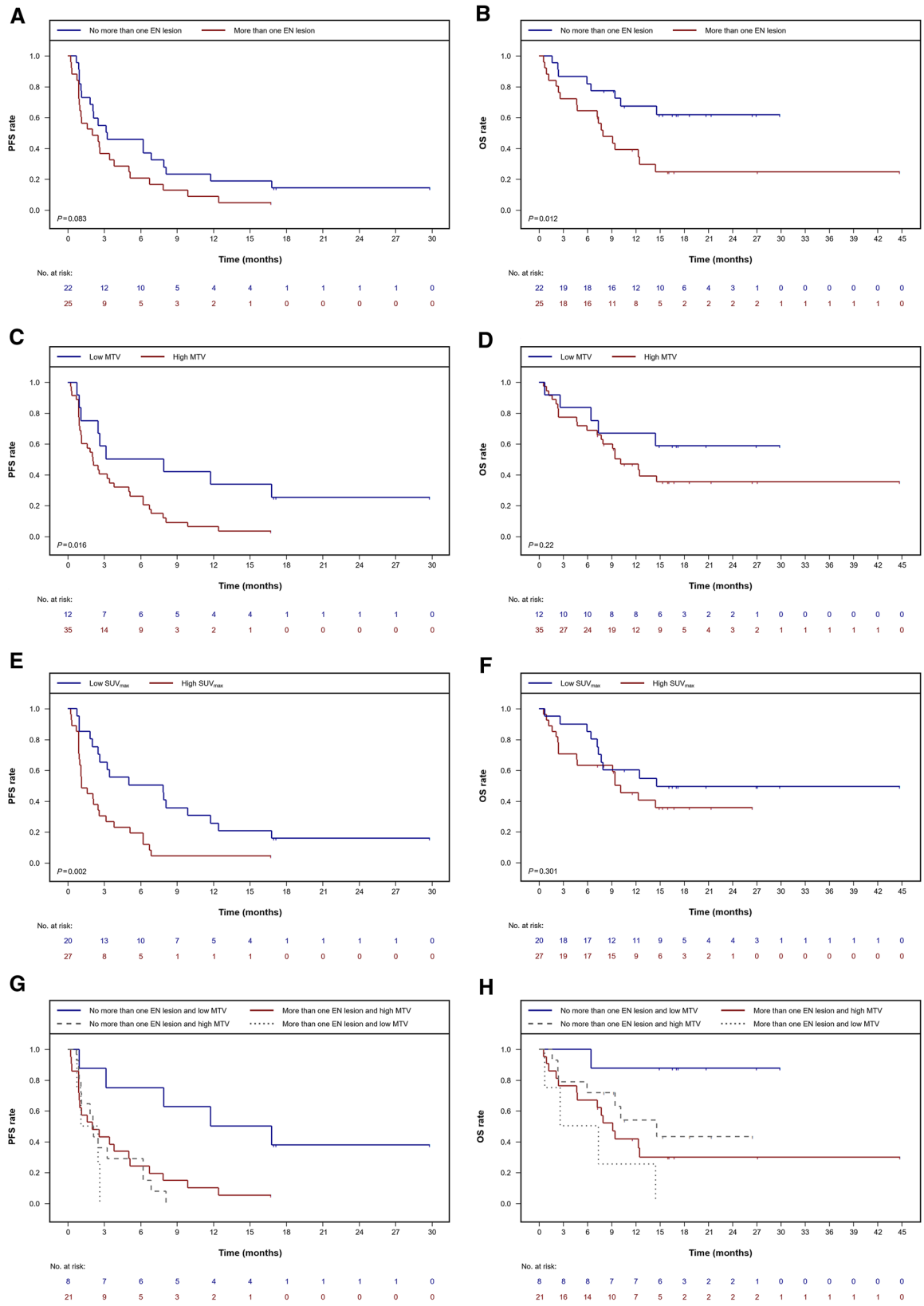

Figure 1. Kaplan–Meier curves for PFS as well as OS according to (A, B) EN disease status, (C–F) PET parameters, and (G, H) combined risk stratification. EN = extra-nodal; MTV = metabolic tumor volume; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; SUV_{max} = maximum standardized uptake value.

was 44 mL in our cohort (range 0–1831 mL). Based on the AIC score, we selected a tumor volume of 11 mL as optimal threshold regarding PFS with a HR of 2.57 (95% CI 1.16-5.67). ROC analysis confirmed this cut-off and revealed a sensitivity and specificity of 75.0% and 79.1%, respectively (Figure 2).

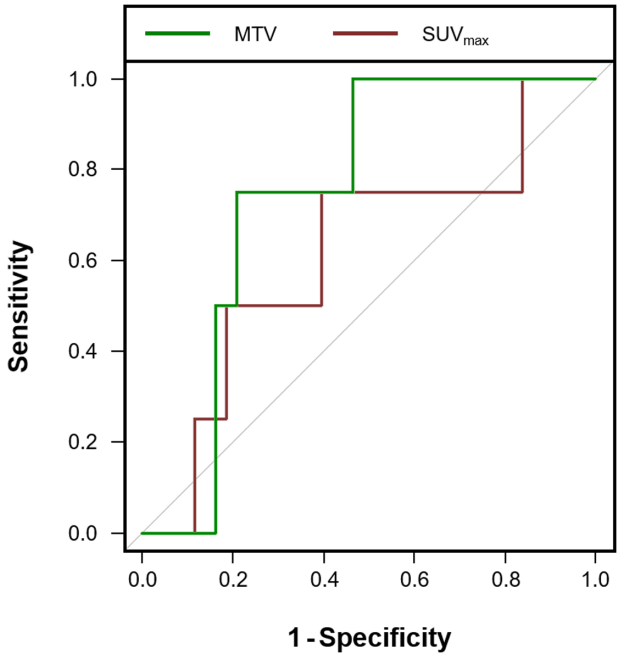

Figure 2. ROC curves for predicting PFS based on PET parameters. MTV = metabolic tumor volume; PET = positron emission tomography; PFS = progression-free survival; ROC = receiver operating characteristic; SUV_{max} = maximum standardized uptake value.

One-year PFS and OS probability was 5.7% (95% CI 1.5-21.9%) and 46.6% (95% CI 32.3-67.3%), respectively, for individuals with elevated MTV (Figure 1C and D). In contrast, patients who had lower tumor load achieved a significantly superior PFS (P = 0.016) with 33.3% (95% CI 15.0-74.2%) free of disease progression and death after 12 months, while the one-year OS probability was 66.7% (95% CI 44.7-99.5%, P = 0.22). However, we did not observe any association between higher metabolic tumor burden and the development of CRS (r = 0.015) or ICANS (r = 0.044).

High MTV and EN disease were weakly correlated (r = 0.27) and can thus be considered as independent predictors of survival. A particularly favorable outcome was noted for patients with no risk factors who had one-year PFS and OS rates of 50.0% (95% CI 25.0-100%) and 87.5% (95% CI 67.3-100%), respectively (Figure 1G and H). Moreover, SUV_{max} predicted one-year PFS (P = 0.002), but not OS (P = 0.301), after CAR T-cell treatment when using the optimal threshold of 16.7 (Figure 1E and F).

DISCUSSION

CAR T-cell therapy heralds a fundamental shift in the management of relapsed and refractory large B-cell lymphomas. However, this novel cellular treatment requires specialized infrastructure as well as complex patient preparation and carries a risk of relevant toxicities.[19] Thus, candidates should be selected carefully according to individual factors that are currently under investigation. Tumor load before CAR T-cell therapy, either measured through the surrogate parameter LDH or using CT based on the Lugano criteria, has emerged as an independent predictor of outcome.[5,20,21] However, besides these indirect and rather imprecise methods to quantify the extent of disease, metabolically active lymphoma burden can be accurately assessed by PET.

Our study shows that higher MTV is associated with inferior one-year PFS following CAR T-cell treatment. A similar observation has been made by Dean et al[16] who additionally report significantly shorter OS for individuals with elevated metabolic lymphoma burden. Unlike these authors, we did not categorize patients by median of MTV but identified a markedly lower tumor volume as most predictive. Another small retrospective analysis suggested a similarly low MTV threshold for the specific context of CAR T-cell treatment.[22] The association of higher metabolic tumor load with CRS development, reported by a group from China, could not however be observed in our study.[23] Recently, tumor and systemic immune dysregulation have been described as forming a potential mechanistic link between elevated lymphoma burden and lower response rates.[24] These findings indicate that effective reduction of tumor load before final product administration is particularly important in patients with higher MTV. Hence, the value of debulking should be investigated more thoroughly. While the recent study by Lutfi et al[25] found no association between bridging therapy and survival benefits but instead revealed a link to prolonged cytopenia, others report favorable outcome, especially for individuals achieving deep remission before their planned treatment.[26,27] We performed PET prior to lymphodepleting chemotherapy in all except one patient who was scanned on the day of product infusion. This is a time point at which cytoreductive treatment can still be considered if the individual has high MTV. Moreover, systemic and radiotherapy shortly after CAR T-cell administration may be feasible alternatives in heavily pretreated cases.

Multivariable analysis identified EN disease as the most predictive of conventional tumor and patient characteristics, with significantly shorter OS after therapy. Similar results have been published by Vercellino et al[17] who examined the larger French cohort and proposed a model based on EN involvement as well as high metabolic lymphoma burden. Lesions in the skeleton, lung, liver, or skin may be more difficult to penetrate for CAR T-cells which reduces their efficacy at these tumor sites independent of MTV. Some studies on solid cancers have already shown that the migration of T-cells into extra-lymphatic tissue is limited.[28] Alternative strategies are therefore required to enhance the penetration of CAR T-cells. Interestingly, our results also confirm findings reported by Cohen et al[29] regarding the predictive value of SUV_{max} before product administration. However, the association between elevated CRP and shorter PFS observed within another French cohort could not be validated in our patients.[30]

A further important conclusion which emerged from the present analysis was that MTV can be measured reliably with an SUV threshold of 4.0 even by two observers using different software tools for tumor delineation. In a recently published study, the highest concordance has been achieved through cut-offs such as SUV 2.5 and 4.0, thereby also supporting the argument for fixed thresholds.[31] Barrington et al[32] showed a significantly higher success and lower failure rate for the cut-off we applied.

Several limitations of this work should be considered when interpreting the results: Our analysis is retrospective in nature and covers a limited follow-up time. Moreover, construct-specific subgroup analyses were not possible, since we included a rather low number of patients treated for various diagnoses, including transformed follicular lymphoma. It is already known that certain co-stimulatory domains promote rapid CAR T-cell expansion.[33] Correlation between metabolic tumor burden and kinetic parameters is likely to improve our understanding of response heterogeneity. Future research should particularly examine whether the optimal MTV thresholds differ between constructs, as this PET-derived biomarker might then be a valuable parameter for product selection.

In conclusion, MTV could guide therapy by identification of those individuals likely to benefit from upfront debulking. It might also become useful for defining the optimal CAR T-cell infusion time point. Moreover, our study found a risk profile, including higher tumor load and SUV_{max} as well as EN disease, that should be considered in the management of candidates, since these factors are associated with significantly inferior patient outcome.

AUTHOR CONTRIBUTIONS

C-AV, PG, and CH conceptualized the study. SF performed statistical analysis. C-AV, PG, SF, and CH drafted the manuscript. All authors provided patients or collected data, participated in revising the manuscript, and approved its final version.

DISCLOSURES

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