Day 30 $SUV_{max}$ Predicts Progression in Lymphoma Patients Achieving PR/SD After CAR T-cell Therapy

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Abstract:
About 70% of patients with large B-cell lymphoma (LBCL) treated with axicabtagene ciloleucel (axi-cel) who achieve a partial response (PR) or a stable disease (SD) on day 30 (D30) PET-CT scan progress, but predictive factors of progression are unknown. This a retrospective study of patients with LBCL treated with axi-cel at MD Anderson Cancer Center between 01/2018 and 02/2021. Among 50 patients with D30 PR/SD, 13 (26%) converted to complete response (CR). Among 95 patients with D30 CR, 72 (76%) remained in CR. On univariate analysis, the only day -5 characteristic associated with conversion from D30 PR/SD to subsequent CR was a higher platelet count ($p=0.05$). The only D30 factor associated with conversion from D30 PR/SD to subsequent CR was lower D30 $SUV_{max}$ ($p<0.001$), and all patients with and D30 $SUV_{max} \geq 10$ progressed. After a median follow-up of 12 months, no significant difference in median progression-free survival was observed when comparing patients who converted from D30 PR/SD to subsequent CR to those who had been in CR since D30 ($p=0.19$). Novel predictive and prognostic markers based on tissue biopsy and non-invasive diagnostic assays are needed to more effectively identify these patients and characterize the biology of their residual disease.

Conflict of interest: COI declared - see note

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Day 30 SUV\textsubscript{max} Predicts Progression in Lymphoma Patients Achieving PR/SD

After CAR T-cell Therapy

Running title: CAR T-cells and D30 PR/SD

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Key Points

- Patients with D30 PR/SD with subsequent conversion to CR experience similar early outcomes as patients who achieved CR by D30.
- $SUV_{\text{max}}$ of 10 or higher may help identify patients with D30 PR/SD at risk of subsequent progression.
Abstract
About 70% of patients with large B-cell lymphoma (LBCL) treated with axicabtagene ciloleucel (axi-cel) who achieve a partial response (PR) or a stable disease (SD) on day 30 (D30) PET-CT scan progress, but predictive factors of progression are unknown. This a retrospective study of patients with LBCL treated with axi-cel at MD Anderson Cancer Center between 01/2018 and 02/2021. Among 50 patients with D30 PR/SD, 13 (26%) converted to complete response (CR). Among 95 patients with D30 CR, 72 (76%) remained in CR. On univariate analysis, the only day -5 characteristic associated with conversion from D30 PR/SD to subsequent CR was a higher platelet count (p=0.05). The only D30 factor associated with conversion from D30 PR/SD to subsequent CR was lower D30 SUV$_{\text{max}}$ (p<0.001), and all patients with D30 SUV$_{\text{max}}$ $\geq$10 progressed. After a median follow-up of 12 months, no significant difference in median progression-free survival was observed when comparing patients who converted from D30 PR/SD to subsequent CR to those who had been in CR since D30 (p=0.19). Novel predictive and prognostic markers based on tissue biopsy and non-invasive diagnostic assays are needed to more effectively identify these patients and characterize the biology of their residual disease.
Introduction

Approximately 40% of patients with relapsed or refractory large B-cell lymphoma (LBCL) treated with chimeric antigen receptor (CAR) T-cell therapy will achieve a durable remission, with similar rates reported across all three products approved by the Food and Drug Administration (FDA).1-4 Patients who are refractory to CAR T-cell therapies, either detected with early clinical or radiological progression observed on day 30 (D30) positron emission tomography (PET)-computed tomography (CT) scan experience very poor outcomes, with an estimated survival of less than 6 months.5 In addition, 70% of patients who achieve either a partial response (PR) or stable disease (SD) on D30 PET-CT will eventually have disease progression, experiencing an equally poor outcome.6 Therefore, a deeper clinical and biological characterization of these patients with D30 PR is necessary to help identify those at risk for progression and to develop optimal consolidation strategies.
Methods

This is a single center retrospective study of all patients with relapsed and/or refractory LBCL achieving PR or SD on D30 PET-CT scan after receiving standard of care axi-cel at MD Anderson Cancer Center (MDACC) between 01/2018 and 02/2021. Data cut-off was 04/2021. The study was approved MDACC Institutional Review Board and conducted in accordance with our institutional guidelines and the principles of the Declaration of Helsinki.

The clinical characteristics and laboratory features before lymphodepleting chemotherapy (D-5) and at time of first PET-CT restaging (D30) were confirmed by review of the medical records. Response status was determined by Lugano 2014 classification. Maximum standardized uptake volume (SUV$_{\text{max}}$) was calculated as previously described, and lesions suspicious for alternative etiologies were excluded from the analysis. The receiver operating characteristic (ROC) method was used for identification of optimal SUV$_{\text{max}}$ thresholds.

Association between categorical variables was evaluated using $\chi^2$ test or Fisher’s exact test. The difference in a continuous variable between patient groups was evaluated by the Mann-Whitney test. Progression-free survival (PFS) was defined as the time from axi-cel to progression of disease, death, or last follow-up (whichever occurred first). Overall survival (OS) was defined as the time from axi-cel infusion to death or last follow-up. PFS and OS were calculated using Kaplan-Meier estimates and compared using the log rank test. A p-value of $\leq$0.05 (two-tailed) was considered statistically significant. Statistical analyses were completed using SPSS 24 and GraphPad Prism 8.
Results and Discussion

On D30, 204 out of 206 treated patients were evaluable for response, and 2 were lost to follow-up. Among the 204 evaluable patients, 102 (50%) achieved CR, 49 (24%) PR, 8 (4%) SD, and 45 (22%) experience either clinical or radiological progressive disease (PD). Among the 57 patients who achieved PR/SD on D30 PET-CT scan, 50 were evaluable for response at D90 or beyond, and were included in the final analysis, 5 were lost to follow-up, and 2 died of unrelated cause before restaging. Among the 50 evaluable patients with D30 PR/SD, 13 (26%) converted to CR on subsequent restaging without additional therapy, and 37 (74%) had progressive disease. Among the 102 patients with D30 CR, 7 were lost to follow-up. In the remaining 95 evaluable patients, 72 (76%) remained in CR at day 90 restaging, and 13 (24%) progressed (Figure 1A).

Baseline characteristics (on D-5) are shown in Table 1. On univariate analysis, the only baseline characteristic associated with conversion from D30 PR/SD to subsequent CR was a higher platelet count (median, 193 vs 128 ×10⁹/L, p=0.05), as a surrogate marker for bone marrow reserve; a trend for association with lower C-reactive protein was also observed (13.7 vs 36 mg/L, p=0.06)(Figure 1B and Supplementary Table 1). No difference in baseline characteristics was observed when comparing patients in CR at D30 to those with PR at D30 who subsequently converted to CR (Supplementary Table 2).

Laboratory, clinical and radiological characteristics collected on D30 are shown in Table 1. On univariate analysis, the only D30 factor associated with conversion from D30 PR/SD to subsequent CR was lower D30 SUV max; median, 5.8 vs 9.8, p<0.001)(Supplementary Table 3). At D30, patients with SUV max < 6, 8/14 (57%) eventually converted to CR, in contrast with patients with SUV max of ≥6 in which 5/36 (14%) converted to CR. All patients with D30 SUV max
≥ 10 had subsequent progressive disease (Figure 1C), and the latter was identified as the optimal threshold (sensitivity 100%, specificity 52%).

After a median follow-up of 12 months (95% CI, 11-13 months), no significant difference in median PFS was observed when comparing the 13 patients with D30 PR/SD and subsequent CR to the 72 patients with D30 CR (1-year PFS rate, 100% vs 84%, p=0.19) (Figure 1D).

Furthermore, no significant difference in median PFS was observed in a landmark analysis at 90 days (p=0.19).

PR/SD on D30 PET-CT scan, defined by a Deauville score of 4-5, can present with a variable range of fluorodeoxyglucose (FDG) avidity, commonly summarized by SUVmax. Other PET-based parameters relevant to patients with active disease include tumor burden, measured as total metabolic tumor volume (TMTV), and the combination of FDG avidity and tumor burden, measured as total lesion glycolysis (TLG). SUVmax, TMTV and TLG have shown prognostic and predictive value in patients with LBCL and among those treated with CAR T-cell therapy, as also shown in this study.9-12 While the availability of TMTV and TLG remains limited, SUVmax is commonly and easily calculated, and may be of significant value in the management of patients with D30 PR/SD, and further investigation of the clinical utility of early intervention among patients treated with CAR T-cell therapy is warranted.

Along with radiological parameters, other non-invasive techniques are currently being developed to identify high-risk patients. For example, circulating tumor DNA detection within the first 30 days of CAR T-cell therapy may allow for early identification of patients who will develop refractory disease; and if still detectable at D30 is associated with poor outcomes.13,14
While the approaches outlined above may help identify patients with D30 PR/SD at risk for progression, the optimal consolidation strategy for these patients remains unknown. Limited data is available regarding the use of third line FDA-approved agents for LBCL patients after CAR T-cell therapy. In this patient population, a response rate of 42-44% has been reported with the use of loncastuximab tesirine and polatuzumab vedotin, respectively.\textsuperscript{15,16} There are no data regarding the efficacy of other third line agents such as tafasitamab and selinexor in this setting.\textsuperscript{17,18} Other promising potential consolidations strategies have been reported with the off-label use of agents that enhance CAR T-cell activity and favorably impact the host tumor immune environment, including ibrutinib, lenalidomide, pembrolizumab and radiation therapy.\textsuperscript{13,19-24}

We acknowledge multiple limitations of this study, including its small sample size, its single center and retrospective nature, and lack of central review for SUV\textsubscript{max} measurements and of more objective measurement, such as TMTV and TLG.

In conclusion, patients with D30 PR/SD that subsequently convert to CR experience similar early outcomes as patients that achieve CR by D30. PET-associated parameters, such as SUV\textsubscript{max} of 10 or higher, may help identify patients with D30 PR/SD at risk of subsequent progression, who may benefit from clinical trials of consolidation therapy. Novel predictive and prognostic markers based on tissue biopsy for patients with D30 PR/SD as well as non-invasive diagnostic assays are needed to more effectively identify these patients and characterize the biology of their residual disease.
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Authorship Contributions

AAZ analyzed data, and wrote the paper; JRW, SAA, LJN, MH, RN, SPI, HJL, RES, CRF, EJS, PK, and SSN provided clinical care to patients and coauthored the paper; GW and HM and collected clinical data and coauthored the paper; LF provided statistical support and coauthored the paper; PS designed the study, analyzed the data, provided clinical care to patients, and wrote the paper.

Disclosure of Conflict of Interest

PS is a consultant for Roche-Genentech, Hutchinson MediPharma and TG Therapeutics, and received research funds from Astrazeneca-Acerta.

RES has received research funding from Seagen, BMS, Rafael Pharmaceuticals and GSK
SA has received research funding from Seattle Genetics, Merck, Xencor, and Tessa Therapeutics and has membership on Tessa Therapeutic’s advisory committee.

LJN reports honoraria from Celgene, Genentech, Gilead, Janssen, Juno, Novartis, Spectrum, TG Therapeutics and research support from Celgene, Genentech, Janssen, Karus Therapeutics, and Merck.

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Tables and Figures

| Total (N=50)                        | Number (%), median [range]          |
|-------------------------------------|-------------------------------------|
|                                     | Day -5                              | Day 30                             |
| DLBCL/HGBCL                         | 41 (82%)                            | --                                 |
| Age (years)                         | 61.5 [18-84]                        | --                                 |
| Male                                | 36 (72%)                            | --                                 |
| ECOG performance status 3-4         | 1 (2%)                              | --                                 |
| Ann Arbor Stage III-IV              | 40 (80%)                            | --                                 |
| Extra-nodal sites > 1               | 31 (62%)                            | --                                 |
| IPI score 3-5                       | 26 (52%)                            | --                                 |
| Absolute neutrophil count (10^9/L) | 2.77 [0-17.36]                      | 1.43 [0-9.97]                      |
| Absolute lymphocyte count (10^9/L)  | 0.61 [0.02-3]                       | 0.43 [0-2.5]                       |
| Absolute monocyte count (10^9/L)    | 0.475 [0-1.11]                      | 0.41 [0-1.05]                      |
| Hemoglobin (g/dL)                   | 10.4 [7.2-14.7]                     | 10.45 [5.7-15.2]                   |
| Platelet count count (10^9/L)       | 140 [6-390]                         | 66.5 [1-270]                       |
| C-reactive protein (mg/L)           | 29.6 [0.37-175]                     | 2.57 [0.15-211]                    |
| Ferritin (mg/L)                     | 661 [33-9694]                       | 947 [7.14-30833]                   |
| Lactate dehydrogenase (U/L)         | 336.5 [128-5323]                    | 214 [107-3693]                     |
| Previous therapies (n)              | 3 [2-7]                             | --                                 |
| Bridging therapy use                | 21 (42%)                            | --                                 |
| Bridging: chemotherapy              | 14 (28%)                            | --                                 |
| Radiation therapy                   | 4 (8%)                              | --                                 |
| Biological therapy                  | 3 (6%)                              | --                                 |
| None                                | 29 (58%)                            | --                                 |
| Refractory disease                  | 42 (84%)                            | --                                 |
| Previous autologous SCT             | 9 (18%)                             | --                                 |
| Previous allogeneic SCT             | 1 (2%)                              | --                                 |
| SUV_{max}                           | 24.9 [3.5-77.7]                     | 7.75 [2.6-35.1]                    |

**Table 1. Baseline characteristics (on day -5 and on day 30)**

DLBCL, diffuse large B-cell lymphoma; HGBCL, high grade B-cell lymphoma; IPI, internal prognostic index; LDH, lactate dehydrogenase; SCT, stem cell transplant.

Pre-CART SUV_{max} was reported only for patients who had a PET-CT performed before lymphodepleting chemotherapy, without interposed bridging therapy.
**Figure 1. Factors associated with conversion of D30 PR/SD to subsequent CR.** A. Rates of conversion to CR among patients with D30 CR and D30 PR/SD; B. Baseline characteristics associated with conversion of D30 PR/SD to D90 CR; C. Association between D30 SUVmax and conversion of D30 PR/SD to D90 CR; D. PFS among patients converting from D30PR to CR as compared to those achieving D30 CR.

None of the patients that converted from D30 PR/SD to subsequent CR experienced progression. All patients with D30 PR and SUV$_{\text{max}}$ of 10 or higher subsequently progressed.

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; SUV$_{\text{max}}$, maximum standardized uptake volume