Axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma patients in complete metabolic response

Axicabtagene ciloleucel (axi-cel) is an anti-CD19 autologous chimeric antigen receptor (CAR) T-cell product approved by the Food and Drug Administration for patients with large B-cell lymphoma (LBCL) who progress or relapse within 12 months of frontline chemoimmunotherapy (CIT) or after two lines of systemic therapy. These approvals are based on results of the ZUMA-7 and ZUMA-1 studies, respectively.[1,2] However, both trials required active lymphoma for eligibility and prohibited bridging chemotherapy, so there are limited data to support the use of axi-cel in patients with complete metabolic response (CMR) on positron emission tomography (PET) scan before CAR T-cell infusion. In real-world practice, the management of patients who achieve CMR before axi-cel infusion remains controversial, with some providers recommending observation or consolidation with autologous stem cell transplant (SCT).[3-7] Concerns regarding axi-cel use in patients achieving CMR also include potentially decreased efficacy, based on the theoretical possibility of suboptimal CAR T-cell expansion in the absence of an adequate number of CD19+ tumor cells. Here, we present a retrospective analysis of 13 patients with relapsed or refractory LBCL who achieved a CMR prior to axi-cel infusion and compare their clinical outcomes and CAR T-cell expansion levels to matched cohorts of patients with active LBCL. We find that patients in CMR at the time of axi-cel infusion had similar rates of cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS), as well as similar progression-free survival (PFS) and overall survival (OS) as patients with active disease. CAR T-cell peak levels were comparable to higher in patients with CMR at the time of axi-cel infusion compared to those with active disease. These findings support the feasibility of axi-cel in patients with relapsed or refractory LBCL who achieve a pre-infusion CMR.

We conducted a retrospective cohort analysis of 240 consecutive patients with relapsed or refractory LBCL treated with standard-of-care axi-cel at our institution between Januray 2018 and December 2021. Of these, 196 had a PET-computerized tomography scan performed after their most recent therapy and before lymphodepleting chemotherapy (LDC). Thirteen of these patients were in CMR at the time of axi-cel infusion. The immediate treatment before achieving CMR consisted of CIT in seven patients (platinum-based in 5 patients, methotrexate-based in 2 patients), radiation therapy in three patients, and targeted therapy in three patients (lenalidomide and rituximab in 2 patients, and ibrutinib in 1 patient). Baseline characteristics are shown in Table 1. Bridging therapy was defined as therapy received after apheresis and before LDC. C-reactive protein (CRP) and ferritin levels were measured at the initiation of LDC.

Of the 183 patients with metabolically active disease, 41 achieved a partial response (PR) prior to axi-cel infusion

Table 1. Baseline characteristics of overall population.

Total (N=196)	SD/PD (N=142)	PR (N=41)	CMR (N=13)	*P* value CMR *vs.* SD/PD	*P* value CMR *vs.* PR
DLBCL/HGBCL, N (%)	105 (74)	29 (71)	10 (77)	0.814	0.664
Age in years, median (range)	59 (21-85)	61 (18-78)	53 (39-72)	0.446	0.485
Male, N (%)	92 (65)	29 (71)	7 (54)	0.432	0.260
ECOG 2-4, N (%)	22 (16)	7 (17)	1 (8)	0.449	0.407
CRP mg/L, median (range)	21.9 (0.3-283.7)	7.1 (0.3-246.2)	7.7 (1.8-29.1)	0.023	0.879
Ferritin mg/L, median (range)	810.5 (13-38,964)	679 (69-3,834)	602 (101-3,190)	0.640	0.671
Previous therapies >2, N (%)	115 (81)	35 (85)	8 (62)	0.097	0.063
Bridging therapy use, N (%)	63 (44)	28 (68)	6 (46)	0.901	0.150
Bridging chemotherapy, N (%)	43 (30)	22 (54)	4 (31)	0.971	0.150
Disease refractory to prior therapy, N (%)	113 (80)	31 (76)	6 (46)	0.006	0.046
Previous autologous SCT, N (%)	34 (24)	5 (12)	4 (31)	0.584	0.117
Previous allogeneic SCT, N (%)	4 (3)	0 (0)	0 (0)	0.540	na

SD: stable disease; PD: progressive disease; PR: partial response; CMR: complete metabolic response; DLBCL/HGBCL: diffuse large B-cell lymphoma/high grade B-cell lymphoma (as compared to transformed follicular lymphoma and primary mediastinal lymphoma); ECOG: European Cooperative Oncology Group; CRP: C-reactive protein; SCT: stem cell transplant; na: not available.

while 142 had stable disease (SD) or progressive disease (PD). When compared to the 13 patients in CMR, patients with SD or PD had higher CRP levels at initiation of LDC (21.9 mg/L *vs*. 7.7 mg/L; *P*=0.023) and more frequently had disease refractory to prior therapy (80% *vs*. 46%; *P*=0.006). Patients with PR also more frequently had disease refractory to prior therapy (76% *vs*. 46%; *P*=0.046) compared to patients in CMR. Therefore, we performed propensity score matching to match cohorts of patients in SD/PD and in PR to patients in CMR based on these covariates (CRP and prior refractoriness for SD/PD; prior refractoriness for PR). A propensity score was calculated using logistic regression and patients in SD/PD were matched 5:1 with patients in CMR while patients in PR were matched 2:1 with patients in CMR. Baseline characteristics of these cohorts are shown in Table 2. No significant differences between the matched cohorts were identified.

When comparing patients in CMR to matched cohorts of patients with SD/PD and PR, there were no significant differences in the rates of CRS of any grade (100% *vs*. 91% *vs*. 91%) and grade 2-4 CRS (62% *vs*. 35% *vs*. 50%). Grade 3-4 CRS was observed in two (15%) patients in CMR, six (9.2%) patients with SD/PD and one (4.5%) patient in PR. There were also no significant differences in the rates of ICANS of any grade (85% *vs*. 59% *vs*. 46%), grade 3-4 ICANS (23% *vs*. 39% *vs*. 36%) and grade 3-4 cytopenias at day 30 (62% *vs*. 57% *vs*. 46%) across groups (Figure 1A).

After a median follow-up of 26 months (95% confidence interval [CI]: 17-35), when comparing patients in CMR to matched cohorts of patients with SD/PD and PR, significant differences for 2-year PFS (44% *vs*. 35% *vs*. 60%) and 2-year OS rates (71% *vs*. 51% *vs*. 63%) were not found (Figure 1B).

CAR T-cell amplification in peripheral blood at day 7 (peak expansion) was measured in seven patients from the cohort in CMR and in 19 patients from the matched cohorts with active disease (17 patients with SD/PD, 2 patients in PR). Significantly higher levels of expansion were observed in patients who achieved CMR (geometric mean [GM] 47.7 cells/μL, coefficient of variation [CV] 124%) compared to patients who did not (GM 5.0 cells/μL, CV 307%; *P*=0.035) (Figure 1C). No CD19+ B cells were detected in peripheral blood at day 0 or day 7 for any of the seven patients in CMR (Figure 1D). All three patients who relapsed and were assessed for CD19 expression were CD19+ at the time of relapse.

In this study, we show for the first time that patients with relapsed or refractory LBCL who achieve pre-infusional CMR and are treated with axi-cel have improved CAR T-cell expansion and comparable safety and efficacy profiles to those with pre-infusional active disease.

Our results are consistent with those of several prior studies. For instance, adequate CAR T-cell expansion has been reported in the JULIET study among seven patients with relapsed or refractory LBCL who achieved CMR before tisagenlecleucel infusion.[8] However, due to significant differences in construct and kinetics, similar findings could not be inferred for axi-cel. Additionally, a recent retrospective study showed significantly prolonged survival in patients with LBCL who had a low total metabolic tumor volume before axi-cel infusion.[9] Our data also suggest that decreasing tumor burden before CAR T-cell infusion does not diminish cell expansion or worsen clinical outcomes. Larger numbers of patients in CMR at time of infusion are needed to better determine the clinical efficacy of axi-cel in this setting.

Table 2. Baseline characteristics of matched cohorts.

Total (N=100)	SD/PD (N=65)	PR (N=22)	CMR (N=13)	*P* value CMR *vs*. SD/PD	*P* value CMR *vs*. PR
DLBCL/HGBCL, N (%)	47 (72)	17 (77)	10 (77)	0.732	0.981
Age in years, median (range)	59 (21-81)	59 (18-72)	53 (39-72)	0.668	0.625
Male, N (%)	41 (63)	17 (77)	7 (54)	0.532	0.149
ECOG 2-4, N (%)	8 (12.3)	5 (23)	1 (8)	0.634	0.254
CRP mg/L, median (range)	7.7 (0.3-283.7)	8.3 (0.3-142.6)	7.7 (1.8-29.1)	0.639	0.987
Ferritin mg/L, median (range)	606.5 (13-14,361)	637 (69-3,834)	602 (101-3,190)	0.856	0.749
Previous therapies >2, N (%)	53 (82)	18 (82)	8 (62)	0.111	0.185
Bridging therapy use, N (%)	28 (43)	15 (69)	6 (46)	0.838	0.199
Bridging chemotherapy, N (%)	18 (28)	13 (59)	4 (31)	0.822	0.105
Disease refractory to prior therapy, N (%)	46 (71)	12 (55)	6 (46)	0.086	0.631
Previous autologous SCT, N (%)	17 (26)	2 (9)	4 (31)	0.732	0.100
Previous allogeneic SCT, N (%)	3 (5)	0 (0)	0 (0)	0.430	na

SD: stable disease; PD: progressive disease; PR: partial response; CMR: complete metabolic response; DLBCL/HGBCL: diffuse large B-cell lymphoma/high grade B-cell lymphoma (as compared to transformed follicular lymphoma and primary mediastinal lymphoma); ECOG: European Cooperative Oncology Group; CRP: C-reactive protein; SCT: stem cell transplant; na: not available.

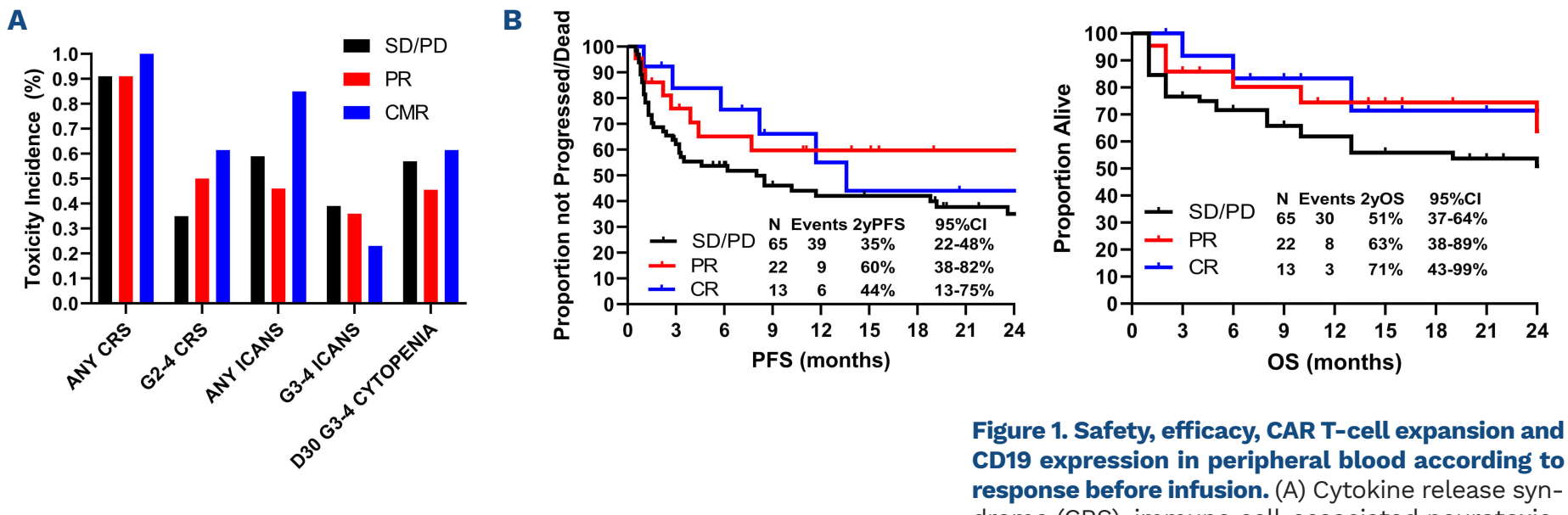

Figure 1. Safety, efficacy, CAR T-cell expansion and CD19 expression in peripheral blood according to response before infusion. (A) Cytokine release syndrome (CRS), immune cell-associated neurotoxicity syndrome (ICANS) and day 30 grade 3-4 cytopenia according to pre-infusion response in matched cohorts. (B) Progression-free survival (PFS) and overall survival (OS) according to pre-infusion (PFS) response in matched cohorts. (C) Day 7 (peak) chimeric antigen receptor CAR T-cell levels among patients with and without pre-infusion complete metabolic response (CMR). (D) CD19 expression on day 0 peripheral blood mononuclear cells from patients with pre-infusion CMR (representative image). SD/PD: stable disease/progressive disease; PR: partial response; CR: complete response; CI: confidence interval.

One mechanism by which high tumor burden may suppress CAR T-cell efficacy is through an increased presence of protumoral macrophages that contribute to an immunosuppressive microenvironment.[10-12] However, it is difficult to determine what role this mechanism plays when residual disease is too small to be detected by PET. The continued presence of an immunosuppressive microenvironment in subclinical residual disease may in part explain why outcomes from patients in CMR are not clearly superior to those in PR or SD/PD. Nevertheless, our data suggest that LBCL patients who achieve a CMR after salvage CIT may still benefit from CAR T-cell therapy, although prospective validation and comparison with autologous SCT in this setting is needed.[13]

One theoretical concern with the use of axi-cel in patients achieving CMR is that the limited presence of tumor cells expressing CD19 would negatively impact CAR T-cell expansion. However, our data suggest that patients in CMR at the time of axi-cel infusion have comparable to high peak CAR T-cell levels than those with active disease. The degree of CAR T-cell expansion is closely related to development of CRS and ICANS.[14] Thus, our finding of high peak CAR T-cell levels in patients in CMR is consistent with our finding that these patients experience similar rates of CRS and ICANS as those with active disease. The robust CAR T-cell expansion noted in patients in CMR may be due in part to a decrease in the immunosuppressive components of the tumor microenvironment as discussed above. Potential sources of antigen driving CAR T-cell expansion in patients achieving CMR include subclinical residual disease and B cells circulating in peripheral blood or residing in lymph nodes or other tissues. Of note, no circulating CD19+ B cells were detected in the peripheral blood of any patient on day 0 or day 7, making these an unlikely source of antigen stimulation. Furthermore, in three patients who relapsed and were assessed for tumoral CD19 expression, all were CD19+ at the time of relapse. This finding suggests that mechanisms other than CD19 antigen loss are responsible for relapse in this patient population. Further investigation is warranted to better understand the kinetics of CAR T-cell expansion and persistence as well as the mechanisms of relapse in these patients.

We acknowledge multiple limitations of this study, including its single-center and retrospective nature, its relatively small sample size and the lack of data regarding measurable residual disease or long-term CAR T-cell persistence in these patients.

In conclusion, our data support the use of axi-cel in patients with relapsed or refractory LBCL who achieve a CMR before axi-cel infusion and warrant further investigation of its activity as a consolidative strategy in future trials. Identification of effective and biologically rational bridging therapies aimed at decreasing disease burden and improving outcomes in patients treated with axi-cel is needed.

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Contributions

APJ and SG analyzed data, and wrote the paper; JW, RES, LEF, SPI, CRF, SA, LJN, PK, EJS and SSN provided clinical care to patients and co-authored the paper; HM, JJ, MN and SH collected clinical data and co-authored the paper; APJ, NPO and SSN performed correlative studies and co-authored the paper; LF provided statistical support and co-authored the paper; PS and YN designed the study, analyzed the data, provided clinical care to patients, and wrote the paper.

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Data-sharing statement

De-identified data are available upon request from the corresponding author.

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