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POSTER ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Impact of "Cell-of-Origin" on Outcome after Axicabtagene-Ciloleucel CAR-T Cell Therapy in Relapsed/Refractory Aggressive Non-Hodgkin B-Cell Lymphomas

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Introduction: Despite significant advances in characterizing aggressive B-cell non-Hodgkin lymphomas (aNHL) based on molecular and genetic signatures, the Hans algorithm, determined by immunohistochemistry, remains the most commonly used approach to differentiate aNHLs based on the cell-of-origin (COO) into germinal center B-cell (GCB) and non-GCB types. Although the Hans algorithm has demonstrated reliability as a predictor of better outcomes in newly diagnosed GCB cases, conflicting evidence has emerged, particularly in the relapsed/refractory (R/R) setting, and there are no definitive data about the impact of COO in patients (pts) receiving CAR-T cells. Thus, we conducted a retrospective analysis to evaluate the impact of COO extended to R/R aNHLs who underwent treatment with axicabtagene-ciloleucel (axi-cel).
Methods: We retrospectively collected data from pts with R/R aNHLs treated with axi-cel at Fred Hutchinson Cancer Center between February 2018 and August 2022. The Hans algorithm, using CD10, BCL6 and MUM1 markers, was employed to stratify the pts into two cohorts: GCB and non-GCB. Paired biopsies of diagnosis and relapse before CAR-T eligibility were reviewed at our institution. Response to CAR-T was assessed at one month per Lugano PET/CT criteria.
Univariate cox proportional hazard regression was used to estimate associations between baseline factors and outcomes. Statistically significant factors ($p<.05$) in univariate analysis were further evaluated by multivariate analysis. Continuous variables were compared by Mann-Whitney U test and categorical variables by Fischer's exact test. Progression-free survival (PFS) was calculated from the date of CAR-T cell infusion to the date of death from any cause, disease progression or relapse. Overall survival (OS) was calculated from the date of CAR-T cell infusion to the date of death from any cause.
Results: Sixty-four pts were included in this analysis, with an equal distribution of pts in the two cohorts: 32 with GCB subtype and 32 with non-GCB subtype. Baseline pts' characteristics and histology subtypes are listed in Table 1. Transformed follicular lymphoma and primary mediastinal B-cell lymphoma were not included in this analysis. The presence of bulky disease (defined as >5cm diameter) was higher in the GCB subtype (56% vs 22%, $p<.001$). Although primary refractory cases were more frequent in the GCB cohort (87.5 vs 66%), statistical significance was not reached (NR)($p=.07$). The same proportion of pts received bridging therapy in the two groups (53% vs 53%, $p=.99$). Pts evaluable for response assessment were 62. Median time to best response was 29 days (range, 21-186) for GCB pts and 31 days (range, 22-182) for non-GCB pts ($p=.91$). The overall response rate was 70% for GCBs (34.5% complete response [CR], 34.5% partial response [PR]) and 75% for non-GCBs (44% CR, 31% PR). After a median follow-up of 24.5 months (range, 9-121), comparable outcomes were observed for both the COO groups: despite the estimated median OS of 14 months (95% CI, 4.73-NR) for GCB vs 40 months (95% CI, 12.55-67.46) for non-GCB, we did not find any significant differences ($p=.73$) (Figure 1A). Estimated median PFS was 10 months (95% confidence interval [CI], 3.5-16) for GCB and 11 months (95% CI, 0-24) for non-GCB ($p=.57$) (Figure 1B). The 2-year OS and PFS were: GCB, 45% (95% CI, 30-69) and 44% (95% CI, 29-67) respectively; non-GCB, 55% (95% CI, 38-79) and 29% (95% CI, 16-55), respectively.

Treatment-related toxicities did not differ between GCB and non-GCB, with cytokine-release syndrome rates of 97% vs 94% (p=.99) and neurotoxicity rates of 53% vs 62.5% (p=.61), respectively. The incidence of infectious complications was 25% vs 19% (p=.76).
On univariate analysis, the impact of COO on OS (HR=0.82, 95% CI 0.39-1.73, p=.60) and PFS (HR=1.18, 95% CI 0.61-2.28, p=.62) was undetermined. After adjusting for bulky disease, elevated LDH, absolute lymphocyte count≤1000/uL, performance status≥2, >2 lines of therapy and response status before axi-cel infusion, the impact of COO on OS (adjusted HR [aHR]=1.73, 95% CI 0.71-4.22, p=.23) and PFS (aHR=2.01, 95% CI 0.93-4.35, p=.08), remained undetermined.
Conclusion: We could not confirm an association between COO, as determined by Hans algorithm, and outcomes in R/R aNHLs who received axi-cel at our center. Prospective analyses on larger datasets and other types of CAR-T products are needed.

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Table 1. Patients' baseline characteristics, overall and by subtype

Characteristic	Overall patients, n = 64	GCB n = 32	Non-GCB n=32	p-value[1]
Age (years), Median (Range)	61 (29-74)	62 (29-74)	60 (34-74)	0.73
Age > 60 years, n (%)	42 (66%)	19 (59%)	16 (50%)	0.62
Male sex, n (%)	25 (58%)	22 (69%)	20 (63%)	0.79
Disease subtype, n (%)				0.32
DLBCL, NOS	47 (73%)	21 (66%)	26 (81%)	
DLBCL/HGBCL	6 (9%)	5 (15.5%)	1 (3%)	
HGBCL	8 (13%)	5 (15.5%)	3 (10%)	
EBV DLBCL	1 (2%)	0	1 (3%)	
FL3B	2 (3%)	1 (3%)	1 (3%)	
ECOG PS>2, n (%)	8 (12.5%)	5 (15.5%)	3 (10%)	0.71
Stage				0.34
Localized (I-II)	12 (19%)	8 (25%)	4 (12.5%)	
Advanced (III-IV)	52 (81%)	24 (75%)	28 (87.5%)	
Elevated LDH (≥210 U/L), n (%)	31 (48%)	15 (47%)	16 (50%)	0.99
Bulky (≥5 cm), n (%)	25 (39%)	18 (56%)	7 (22%)	**<0.001**
Extranodal, n (%)	36 (56%)	16 (50%)	20 (62.5%)	0.45s
≥2 extranodal sites	24 (37.5%)	10 (31%)	14 (44%)	0.44
B-Symptoms	30 (47%)	16 (50%)	14 (44%)	0.8
IPI				0.8
0-2	32 (50%)	17 (53%)	15 (47%)	
3-5	32 (50%)	15 (47%)	17 (53%)	
>2 lines of therapy before CAR-T	25 (39%)	12 (37.5%)	13 (41%)	0.99
Any CRS, n (%)	61 (95%)	31 (97%)	30 (94%)	0.99
Any ICANS, n (%)	37 (58%)	17 (53%)	20 (62.5%)	0.61
Infections, n (%)	14 (22%)	8 (25%)	6 (19%)	0.76
Bridging therapy	34 (53%)	17 (53%)	17 (53%)	0.99

[1]Mann-Whitney U-test, Fischer's exact test. Abbreviations: CRS, cytokine release syndrome; DLBCL, NOS, diffuse large B-cell lymphoma; DLBCL/HGBCL, diffuse large B-cell lymphoma/high grade B-cell lymphoma; EBV DLBCL, Epstein-Barr virus-positive diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL3B, follicular lymphoma grade 3B; GCB, germinal B center; HGBCL, high grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IPI, International Prognostic Index; LDH, lactate dehydrogenase; non-GCB, non-germinal B center.

Figure 1. Kaplan-Meier Curves stratified by Cell-of-Origin. A) Overall survival; B) Progression-free survival.

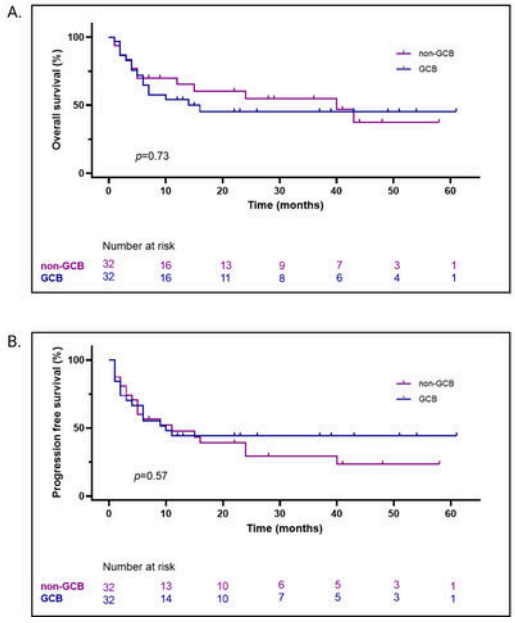

Figure 1

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