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POSTER ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Cladribine and Cyclophosphamide Lymphodepletion Prior to Axicabtagene Ciloleucel in Relapsed or Refractory Large B-Cell Lymphoma

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Introduction: Chemotherapy-based lymphodepletion (LD) with fludarabine and cyclophosphamide (Flu/Cy) is a standard preparatory step for chimeric antigen T-cell (CAR T) therapy and its importance for optimal CAR T expansion and efficacy is well-established. An international Flu shortage required our center and others to utilize alternative agents for LD or risk interruption in patient therapy. When unable to utilize Flu as part of the LD regimen for patients with relapsed/refractory large B-cell lymphoma (RR LBCL) that required CD19-directed CAR T as a standard of care therapy, our center adopted a standard operating procedure to substitute Flu with Cladribine (Clad), an alternate purine analogue with similar chemical structure, as part of Clad/Cy LD prior to axicabtagene ciloleucel (axi-cel). Here we report outcomes in these patients.

Methods: We performed a retrospective, single-center analysis of consecutive RR LBCL patients who received Clad/Cy LD prior to axi-cel at Moffitt Cancer Center between 8/2022 and 1/2023, and compared outcomes to a historical cohort, consisting of 144 Flu/Cy axi-cel LBCL patients treated between 11/2017 and 2/2021. The Clad/Cy LD regimen, given as standard care, maintained Cy at 500 mg/m ^{2} and substituted Flu 30 mg/m ^{2} with Clad 5 mg/m ^{2}/day with both agents given on Days -5, -4, and -3. For efficacy we compared best overall response (BOR) at 90 days and progression-free survival (PFS) comparing the two LD regimens. For safety we compared the rates of cytokine release syndrome (CRS) and neurotoxicity as graded by ASTCT criteria. We also performed correlative analyses exploring absolute lymphocyte count (ALC) kinetics, axi-cel expansion by quantitative PCR, and changes in the cytokine milieu as assessed by the enzyme-linked immunosorbent Ella™ system (Bio-Techne, Oxford, UK) at serial time points following infusion.

Results: 23 patients received Clad/Cy LD followed by axi-cel for R/R DLBCL. Baseline characteristics of the study cohort based on LD are shown in the Table. Compared to the historical cohort, Clad/Cy patients received axi-cel after fewer lines of treatment (median 2 [range, 1-3] vs 2 [range, 1-7]; Rank-Sum test $p<0.01$) and had a greater proportion of relapsed (not refractory) disease (52% vs 22%, $p<0.01$). The 90-day BOR did not differ between the Clad/Cy and Flu/Cy groups (79% vs 84%; P=0.54) with a similar distribution of complete (22% vs 24%) and partial responders (57% vs 60%). With a median follow-up of 4.6 (95% CI, 3.2-6.2) months for Clad/Cy and 24.2 (95% CI, 21.5-25.8) months for Flu/Cy cohorts, PFS was similar (Figure 1B, Log-Rank p=0.84). Rates of CRS grade ≥ 2 were higher in the Clad/Cy cohort (70% vs 44%; p=0.02), but no CRS grade ≥ 3 was observed in the Clad/Cy compared to 13 (9%) of Flu/Cy patients, including three grade 5 events. Neurotoxicity ≥ grade 2 (44% vs 43%; p=0.77) and peak C-reactive protein levels (15 vs Flu/Cy 12; p=0.3) did not differ for the Clad/Cy and Flu/Cy cohorts. Both regimens had comparable peak axi-cel copy numbers (Clad/Cy 7.9 × 10 ^{6} vs Flu/Cy 5.1 × 10 ^{6} copies/μg).

Clad/Cy resulted in a predictable decrease in the ALC from Day -5 to Day 0, but a less profound degree of lymphopenia on Day 0 (0.04 vs 0.02; p<0.01) with ALC 0 achieved later (Day +2 [IQR, +1 to +4] vs Day +1 [IQR, -1 to +2] for Flu/Cy). The median magnitude of change of cytokine levels (Delta = Day -5 - Day 0 concentration) differed between Clad/Cy and Flu/Cy for all tested analytes except IL-6 (3.4 vs 4.6 pg/mL for Flu/Cy; p=0.29). Clad/Cy resulted in greater increases in IL-2 (0.5 vs 0.2 for Flu/Cy; p=0.01) and GM-CSF (2.0 vs 0.9 for Flu/Cy; p=0.03), whereas Flu/Cy had higher IL-15 (31.4 vs 16.8 for Clad/Cy; p<0.01). Interestingly, IFN-γ tended to increase in Clad/Cy and to decrease in Flu/Cy (1.2 vs 0.0; p=0.01).
Conclusions: Clad/Cy LD is feasible for axi-cel conditioning in the treatment of RR LBCL. Although it resulted in less profound LD on the day of CAR T infusion, a later ALC nadir, and a different cytokine milieu compared to Flu/Cy, it was associated with similar peak axi-cel expansion and, at short term follow-up, there appears to be similar initial efficacy and toxicity. Future analyses focusing on response durability and long-term toxicities such as infections and post-CAR T cytopenias are warranted.

Disclosures Shah: *Moffitt Cancer Center:* Current Employment; *Takeda, AstraZeneca, Adaptive Biotechnologies, BMS/Celgene, Novartis, Pfizer, Amgen, Precision Biosciences, Kite/Gilead, Jazz Pharmaceuticals, Century Therapeutics, Deciphera, Autolus Therapeutics, Lilly, Pepromene:* Consultancy; *Celgene, Novartis, Pfizer, Janssen, Seattle Genetics, AstraZeneca, Stemline Therapeutics, Kite/Gilead:* Other: Travel, Accommodations, Expenses; *DSMC, Pepromene Bio:* Membership on an entity's Board of Directors or advisory committees; *Incyte, Jazz Pharmaceuticals, Kite/Gilead, SERVIER:* Research Funding; *Pharmacyclics/Janssen, Spectrum/Acrotech, BeiGene, Gilead Sciences:* Honoraria. **Bachmeier:** *Kite Pharma:* Consultancy. **Nishihori:** *Medexus:* Speakers Bureau; *Moffitt Cancer Center:* Other: Personal fees from Karyopharm and Novartis outside the submitted work. **Lazaryan:** *Sanofi:* Consultancy, Other: Consultancy/speaker and scientific advisory board. **Liu:** *BioLineRx:* Membership on an entity's Board of Directors or advisory committees. **Davila:** *Adicet:* Consultancy; 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OffLabel Disclosure: Cladribine used as part of lymphodepletion regimen prior to axicabtagene ciloleucel

	Clad/Cy (N = 23)	Flu/Cy (N = 144)	*P*-value
Age, years			
Median (range)	67 (50-80)	65 (19-79)	0.11
Male sex	14 (61%)	81 (56%)	0.68
ECOG ≥2	2 (9%)	34 (24%)	0.17
Disease stage III/IV	17 (74%)	113 (79%)	0.60
LDH > upper limit of normal	18 (78%)	93 (65%)	0.24
≥2 extranodal sites	3 (13%)	60 (42%)	<0.01
International Prognostic Index			
0-2	6 (26%)	58 (40%)	0.25
3-5	17 (74%)	86 (60%)	
Disease type			
Double/triple-hit	4 (17%)	27 (19%)	0.68
GCB	18 (78%)	87 (60%)	0.46
Non-GCB	5 (22%)	40 (28%)	
Bulky disease (≥ 10 cm)	7 (30%)	26 (19%)	0.20
Prior therapies			
Median No. of prior lines (range)	2 (1-3)	2 (1-7)	<0.01
≥3 prior lines of therapy	8 (35%)	60 (42%)	0.53
Prior anti-CD19 therapy	1 (4%)	3 (2%)	0.68
Prior autoHSCT	1 (4%)	24 (17%)	0.20
Prior alloHSCT	0 (0%)	2 (1%)	1.00
Bridging/Holding therapy	12 (52%)	94 (67%)	0.16
History of primary refractory disease	10 (43%)	55 (38%)	
Refractory to most recent therapy	1 (4%)	57 (40%)	<0.01
Relapsed	12 (52%)	32 (22%)	
Platelets < 75,000/μL	3 (13%)	9 (6%)	0.22
DVT/PE within 6 months	2 (9%)	11 (8%)	0.70
History of CNS disease	2 (9%)	7 (5%)	0.36
Renal insufficiency (eGFR < 60)	1 (4%)	16 (11%)	0.50
LVEF < 50%	1 (4%)	1 (1%)	0.26
Bilirubin > 1.5 g/dL	0 (0%)	1 (1%)	1.00

GCB, germinal center B-cell; HSCT, hematopoietic stem cell transplant; DVT/PE, deep vein thrombosis/pulmonary embolism; CNS, central nervous system; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

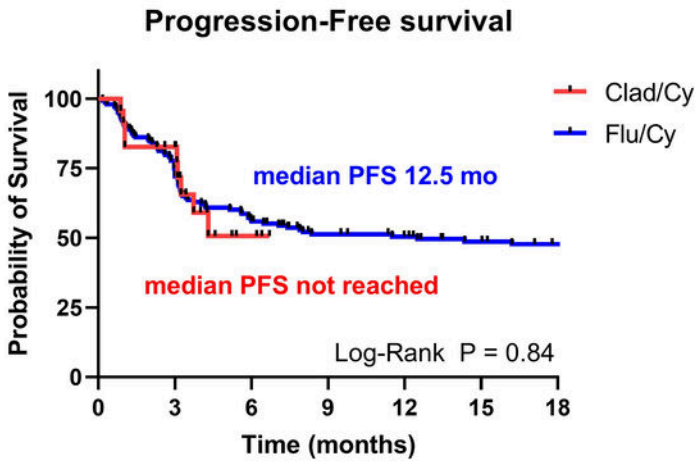

Figure 1

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