Baseline CRP and Ferritin Identify DLBCL Patients at High Risk of Poor Outcomes after Axicabtagene Ciloleucel

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Background

- Despite encouraging efficacy, only ~40% of patients with diffuse large B cell lymphoma (DLBCL) achieved a durable remission following CD19 CAR T cell therapy underscoring the need for early identification of patients at risk of CAR T cell therapy failure or development of severe toxicities (1).
- We and others have reported the role of cytokines and the tumor microenvironment on the development of severe grade >3 toxicities and CAR T resistance in recipients of CD19 targeted therapy (2). However, these analyses are not readily available outside of research settings.
- The aim of this study is to evaluate pre-infusion factors, specifically C-Reactive Protein CRP and Ferritin, associated with development of severe immune mediated toxicities and treatment resistance in patients with R/R DLBCL treated with standard of care axicabtagene ciloleucel (axi-cel)

Methods

- This is single center retrospective analysis of 136 patients treated at Moffitt with axi-cel after ≥2 lines of therapy
- Baseline samples of CRP, LDH and Ferritin were collected within 1 week prior to lymphodepleting (LD) chemotherapy. Cytokine analyses were performed as previously described (2). Cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS) were graded as per ASTCT Criteria (3).
- Patients were risk stratified into three risk groups based on baseline CRP and Ferritin. Low risk (CRP <4mg/dL and Ferritin <400ng/mL), intermediate risk (not meeting either category), and high risk (CRP≥4 mg/dL and Ferritin ≥400ng/mL).
- During the study period, institutional clinical standards were revised to administer prophylactic corticosteroids consecutively to all patients meeting high risk criteria (n=10).
- Patient characteristics were summarized using descriptive statistics,. The associations between continuous variables and the risk groups were assessed using Kruskal-Wallis tests. The associations between categorical variables and three endpoints were evaluated using Chi-squared tests or Fisher's exact tests Patient survival outcomes were compared using Kaplan-Meier curves and subsequent log-rank tests.
- Findings were validated using an international independent data set of patients treated on the pivotal Zuma-1 Trial which included a total of 151 patients enrolled in cohorts 1,2,4 and 6. (4)

References/Disclosures

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Patient Characteristics and Outcomes

	All patients (n=136)	Low risk patients (n=62)	Intermediate Risk (n=47)	High risk Patients (n=27)	P value
Age - Median (Range) yrs	65 (19-79)	64 (24-79)	66 (19-79)	65 (28-79)	0.36
Male Sex – no. (%)	77 (57)	33 (53)	29 (62)	15 (56)	0.67
Histology – no. (%)					0.93
de Novo DLBCL	99 (73)	46 (74)	34 (72)	19 (70)	
Transformed Indolent lymphoma	37 (27)	16 (26)	13 (28)	8 (30)	
Ann Arbor Stage III/IV – no. (%)	108 (79)	46 (74)	37 (79)	25 (93)	0.14
IPI ≥ 3 at apheresis – no. (%)	82 (60)	26 (42)	33 (70)	23 (85)	<0.001
Bulky Disease ≥10cm – no. (%)	26 (20)	3 (5)	15 (33)	8 (30)	0.001
Lines of therapy ≥ 3 — no. (%)	72 (53)	27 (44)	28 (60)	17 (63)	0.13
Bridging therapy – no. (%)	86 (65)	27 (46)	35 (76)	24 (89)	<0.001
Prior autologous HSCT– no. (%)	23 (17)	9 (15)	11 (23)	3 (11)	0.41
ECOG >2– no. (%)	32 (24)	5 (8)	14 (30)	13 (48)	<0.001
Metabolic Tumor Volume – Median (range)	66 (2 1334)	32 (2-1275)	115 (2-1221)	319 (6-1334)	<0.001
CRS					
CRS all grades – no. (%)	126 (93)	59 (95)	44 (94)	23 (85)	0.3
Grade ≥ 3 CRS – no. (%)	14 (10)	1 (2)	6 (13)	7 (26)	0.001
Grade 5 CRS—no. (%)	3 (2)	0	1 (2)	2 (7)	0.09
Use of tocilizumab – no. (%)	71 (52)	28 (45)	26 (55)	17 (63)	0.26
Use of steroids – no. (%)	66 (49)	24 (39)	22 (47)	20 (74)	0.01
Neurotoxicity					
ICANS all grades– no. (%)	83 (61)	33 (53)	29 (62)	21 (78)	0.09
Grade ≥3 ICANS– no. (%)	38 (28)	10 (16)	14 (30)	14 (52)	0.002

Results

- Seven patients (26%) in the high-risk group developed severe grade ≥3 CRS as compared to only one patient in the low-risk group (p=0.001). Severe ICANS was observed in 52% of those categorized as high risk compared to 16% in the low-risk group (p=0.002) (**Table 1**).
- Baseline IL6 was significantly associated with severe CRS (0=0.037) and ICANS (p=0.036). Baselin IL6 significantly correlated with risk category (p<0.001) as showed in **Fig. 1.**
- There was statistically significantly difference in overall survival (OS) and progression free survival (PFS) across the three risk groups (**Fig 2A-B**). OS was 6.9 months 14.9 months and not reached in the high, intermediate and low groups, respectively (p <0.001) (**Fig. 2A**). Median PFS was 3, 7.9 months and not reached in the high, intermediate and low groups, respectively (p=0.001 (**Fig. 2B**)
- We validated our findings in an independent validation cohort for patients treated on Zuma-1 clinical trial. There was a statistically significant difference in OS **(Fig. 2C**, p=0.072) and PFS (**Fig. 3D**, p=0.039) across the three risk groups.
- Patients who met criteria as high-risk (n=10) were treated with prophylactic dexamethasone for three days starting on the day of CAR T cell infusion as per Zuma 1 cohort 6. Univariate analysis was used to compare outcomes compared to historical high-risk patients treated as per standard of care (n=27)
- Although most patients developed CRS, none developed severe CRS in the prophylactic dexamethasone group which compares favorably to 26% in the historical cohort of high-risk patients (p=0.16) Severe ICANS was lower (30%) in the prophylactic steroid group as compared to 52% in the historical (p=0.39)

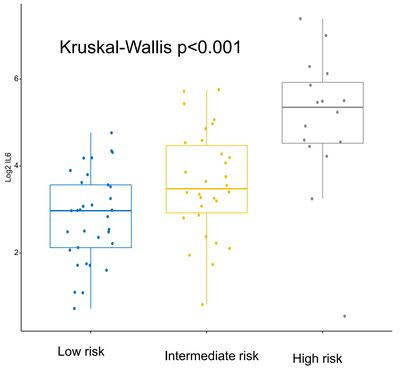

Fig 1. Baseline IL6 levels significantly correlated with risk category based on CRP and ferritin .P value calculated using Kruskal-Wallis.

Discussion

- We show that patients with DLBCL at highest risk of poor outcomes can be easily identified prior to LD using commercially available labs
- Patients in the low risk group have excellent outcomes in terms of toxicity and efficacy and can be managed using standard of care paradigms negating the need for steroid prophylaxis

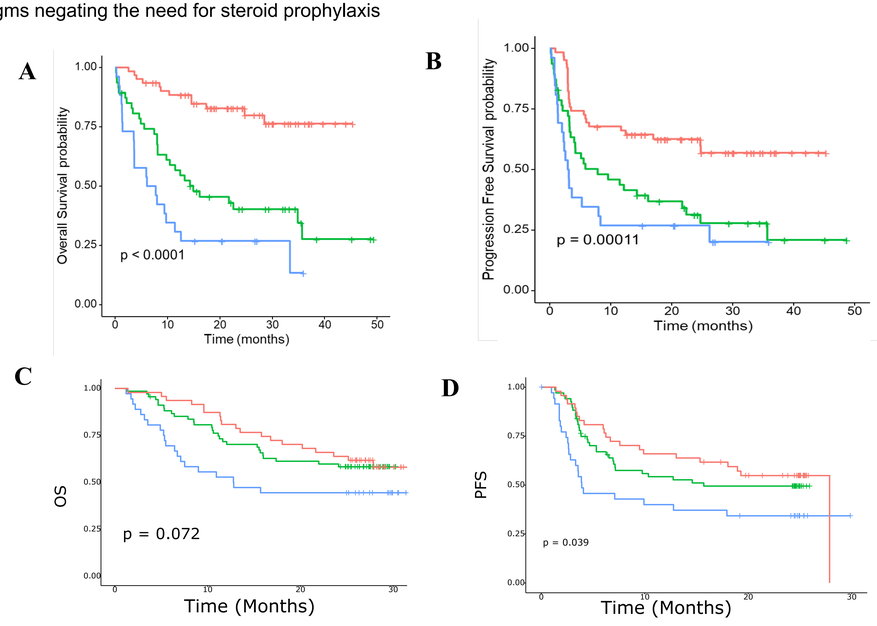

Figure 2: Overall Survival (**A, C**) and Progression Free Survival (**B,D)** in a cohort of 136 patients treated with axi-cel and in a validation cohort (Zuma 1) respectively. Patients stratified as low risk (red), intermediate (green) and high risk (blue) based on baseline CRP and Ferritin.