Eosinophil levels correlate with superior clinical outcomes in high tumor burden DLBCL patients receiving CAR-T therapy

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INTRODUCTION

High tumor burden as measured by tumor volume & tumor metabolic activity is associated with shorter survival & less response to cancer immunotherapies, especially CAR T cell therapies.

However, higher levels of eosinophils -- even higher levels still within the normal range -- as measured in peripheral blood have been associated with greater responses to cancer immunotherapies in lymphoma. (Jia Q, et al 2021).

However, the interaction of elevated peripheral eosinophil levels with tumor burden has not been described.

AIM

This study explores the interaction between:

- baseline WBC subtypes, particularly eosinophils, and tumor burden
- and in predicting best overall response (BOR) and progression-free survival (PFS)

The analysis was done on DLBCL patients undergoing lymphodepleting chemotherapy (LD) prior to anti-CD19 CAR-T cell therapy.

METHOD

We retrospectively analyzed data from 542 DLBCL patients enrolled in clinical trials.

Patients were included if they had:

- recorded tumor burden (sum of longest diameters at screening),
- WBC measurements within 5 days prior to LD, and
- defined BOR and PFS outcomes.

Patients were stratified into high vs. low tumor burden groups using thresholds of greater or lesser than 7 cm for the sum of tumor longest diameters, respectively.

Pre-LD WBC values (monocytes, basophils, eosinophils, neutrophils) were categorized as high or low based on percentile thresholds (monocytes: 20th percentile, basophils: 50th percentile, eosinophils: 30th percentile, neutrophils: 50th percentile).

For each patient, we extracted the last eosinophil count measured before lymphodepletion. Based on these values, we identified the 30th percentile (0.05×10^9/L). Patients with eosinophil counts above this threshold were classified as having a high tumor burden, while those below it were classified as having a low tumor burden.

For BOR, contingency analyses were performed using Fisher's exact test, grouping by:

- WBC category (e.g. high vs low Eosinophils) and
- complete response vs. other responses, or response (complete response and partial response) vs no response (progressive disease, stable disease).

PFS was evaluated using univariate Kaplan-Meier (K-M) analyses with the log-rank test for statistical significance and multivariate Cox Proportional Hazard (CPH) models with the Wald test. For the CPH models we used the pre-LD eosinophils, neutrophils, basophils, the sum of longest tumor diameters, and the number of lines of prior treatment for the entire cohort, and then used only pre-LD WBC values grouped high vs low tumor burden.

RESULTS

Fig 1.CONSORT Diagram from 742 DLBCL patients to the final 542 patients included in the Analysis

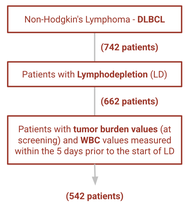


Table 1. Patients Characteristics

Mean (SD) for numerical Count (%) for categorical		Overall	High Eosinophils	Low Eosinophils
	NON-HODGKIN'S LYMPHOMA (DLBCL)	542 (100.0%)	383 (100.0%)	159 (100.0%)
Patients				
Gender	**M**	346 (63.8%)	247 (64.5%)	99 (62.3%)
	F	196 (36.2%)	136 (35.5%)	60 (37.7%)
Race	**WHITE**	461 (85.1%)	326 (85.1%)	135 (84.9%)
	ASIAN	27 (5.0%)	18 (4.7%)	9 (5.7%)
	BLACK OR AFRICAN AMERICAN	22 (4.1%)	16 (4.2%)	6 (3.8%)
	OTHER OR UNKNOWN	20 (3.7%)	18 (4.7%)	2 (1.3%)
	Missing	10 (1.8%)	4 (1.0%)	6 (3.8%)
	AMERICAN INDIAN OR ALASKA NATIVE	2 (0.4%)	1 (0.3%)	1 (0.6%)
BOR	**CR**	301 (55.5%)	227 (59.3%)	74 (46.5%)
	PR	123 (22.7%)	84 (21.9%)	39 (24.5%)
	PD	60 (11.1%)	34 (8.9%)	26 (16.4%)
	SD	47 (8.7%)	33 (8.6%)	14 (8.8%)
	Missing	11 (2.1%)	5 (1.3%)	6 (3.8%)
Age		59.1 (11.7)	59.65 (11.5)	57.75 (12.12)
Number of lines of prior treatment		2.62 (1.52)	2.48 (1.52)	2.96 (1.48)
Sum Longest Diameter (cm) pre infusion		12.0 (8.6)	10.94 (7.75)	14.54 (9.93)

Eosinophils levels Pre Lymphodepletion and Progression Free Survival (PFS)

Multivariate Model (Cox Proportional Hazard Model)

For the multivariate models on the entire cohort, the tumor burden value was the strongest predictor of PFS (p<0.005). Grouping by high vs low tumor burden, multivariate models including eosinophils, basophils, neutrophils and monocytes showed **eosinophils to be correlated with improved PFS in the high tumor burden group (p<0.05).**

Fig 2. Cox Proportional Hazard Model in the High and Low Tumor Burden Groups

Fig 2a. High Tumor burden - 361 patients

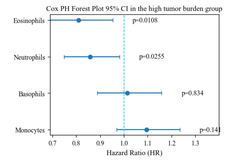
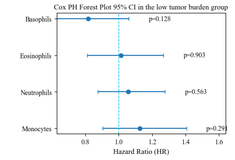


Fig 2b. Low Tumor burden - 181 patients



Univariate Model, separately on the high vs low tumor burden groups (Kaplan-Meier Curves)

In univariate analyses done separately on the high vs low tumor burden groups, **high pre-LD eosinophil levels were significantly associated with improved PFS among patients with high tumor burden** (eosinophils: p<0.01).

Fig 3. Kaplan-Meier Curve for PFS in the High Tumor Burden group, grouped by High vs Low Pre-Lymphodepletion Eosinophils levels (sum of largest diameter >= 7cm)

Fig 3a. High Tumor burden (p<0.01) - 361 patients

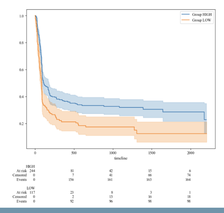
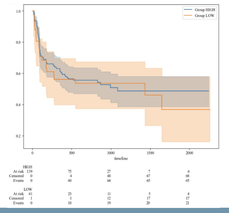


Fig 3b. Low Tumor burden (p = 0.69) - 181 patients



Eosinophils levels Pre Lymphodepletion and Best Overall Response (BOR)

Within the high tumor burden group, high eosinophils levels were associated with superior BOR, defined as either complete response vs. all other responses (p<0.05), or response (complete or partial responses) vs. no response (stable disease or progressive disease) (p<0.05).

In both cases, the odds ratio was less than 1 (0.59 and 0.56, respectively), indicating that **patients with high pre-LD eosinophil counts have higher odds of responding compared to those with low eosinophil counts**.

No significant associations were consistently observed for any other WBC lineages across the analyses conducted.

Fig 4. Best Overall Response in the High Tumor Burden Group (n= 361 patients) grouped by High Vs Low Eosinophils levels pre Lymphodepletion

CONCLUSION

Among DLBCL patients with high tumor burden, elevated eosinophil levels prior to LD for CAR-T cell therapy are associated with improved response rates and PFS, suggesting eosinophils may serve as a predictive biomarker in this high-risk population.

These findings underscore the added value of pre-LD eosinophil levels as a complementary biomarker to tumor burden, offering a more nuanced approach to predicting treatment outcomes and informing CAR-T stratification.

Further studies are needed to determine if the association of peripheral eosinophils with treatment response is a global proxy of immune system health or state, whether the peripheral eosinophils are associated with differences in the tumor micro-environments (i.e., TILs), whether those differences are associated with greater anti-tumor effects mediated by CAR T cells or by the endogenous immune system.

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