The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

TP53 Mutations Detected By Clinical Laboratory Mutation Analysis Predict for Inferior Clinical Outcomes in Patients with Newly-Diagnosed Aggressive B Cell Lymphomas, Including Those with High-Risk Features

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Introduction

While comprehensive genomic analyses have identified genetic subgroups of diffuse large B cell lymphoma (DLBCL) when retrospectively performed on tumor biopsies (bx) from patients (pts) subsequently treated with R-CHOP (PMID 29713087, 29641966), it is unclear if these or similar assays can be applied in clinical practice. We aimed to determine if mutations (mut) detected in bx from newly-diagnosed DLBCL/high grade B cell lymphoma (HGBL) pts by clinical laboratory mutation analysis (CLMA) could predict for clinical outcomes following receipt of first-line therapy.

Methods

Pts with newly-diagnosed DLBCL/HGBL from January 2018-June 2022 whose bx underwent CLMA at the Penn Center for Personalized Diagnostics and received standard-dose R-CHOP or R-EPOCH as first-line therapy were included. Exclusion criteria were death due to non-lymphoma causes during first-line therapy and follow-up <1y after diagnosis if in remission. Pathologic workup of bx was performed as per institutional standard. Therapy was given at the discretion of the treating physician. Data were censored on July 1, 2023.

Results

One hundred thirty-seven pts met inclusion criteria, 15 were subsequently excluded and 117/122 pt bx underwent successful performance of CLMA (96%) with a median turnaround time of 17 days. Baseline characteristics, including mut occurring in ≥10% of cases tested, as well as genetic subgroup classification by LymphGen 2.0 based on available molecular data, are listed in the Table. R-CHOP was received by 72% of pts and R-EPOCH 38% of pts.

The overall response rate (ORR) was 84% (complete response rate [CRR] 69%), and with a median follow-up of 31.3 months, estimated (est) 2 year (y) progression free survival (PFS), est 2y overall survival (OS) and est median OS post-relapse were 70%, 83% and 21.4 months (mo), respectively. Univariate analysis (UVA) identified HGBL classification, *MYC* rearrangement (R) and *TP53* mut as significantly predictive of progression at 2y; however, only *TP53* mut remained predictive on multivariate analysis (MVA) (HR 2.3, 95% CI 1.1-4.8, $P=0.03$). Additionally, UVA identified International Prognostic Index (IPI) score ≥3, HGBL classification, *MYC*-R, MYC-BCL2 double hit lymphoma, *TP53* mut and *TNFRSF14* mut as significantly predictive of death at 2y; however, only HGBL classification (HR 5.0, 95% CI 1.1-22.7, $P=0.04$) and *MYC*-R (HR 4.4, 95% CI 1.0-18.0, $P=0.04$) remained predictive on MVA.

Given that *TP53* mut predicted for both progression and death at 2y, we further analyzed bx with this mut. Forty-seven *TP53* mut were detected in 42 pt bx, and were characterized as missense (mis) in 34, frameshift (fs) in 5, nonsense (non) in 5 splice site (ss) in 2 and other in 1. Thirty-eight (81%) *TP53* mut were deemed loss of function (LOF), either as a mis/non mut designated as non-functional and/or LOF through The *TP53* Database (https://tp53.isb-cgc.org/) or a fs/ss mut (PMID 22955915). Characteristics of pts with and without *TP53* mut are listed in the Table.

Significantly lower rates of ORR (71% vs 90%, $P=0.009$), CRR (55% vs 77%, $P=0.01$), est 2y PFS (57% vs 77%, $P=0.006$), est 2y OS (70% vs 91%, $P=0.001$) and est median OS post-relapse (6.1 mo vs not yet reached, $P=0.001$) were achieved by pts with vs without any *TP53* mut. Est 2y PFS was 70% vs 33% ($P=0.01$) and 2y OS was 85% vs 43% ($P=0.001$) for pts with any *TP53* mut treated with R-CHOP vs R-EPOCH. Additional analysis incorporating LOF status for *TP53* mut revealed that for pts with

Table

Characteristic	All (n=117)	No TP53 mut (n=75)	TP53 mut (n=42)	P
Median age (years)	63	58	65	0.08
International Prognostic Index score ≥3	42%	35%	57%	0.03
HGBL histology	19%	12%	31%	0.02
Prior indolent lymphoma	15%	15%	14%	1.00
Non-GCB cell of origin	50%	46%	57%	0.33
MYC rearrangement	20%	14%	31%	0.05
MYC-BCL2 double hit	9%	7%	14%	0.33
TP53 mutation	36%	---	---	---
SOCS1 mutation	25%	28%	19%	0.37
B2M mutation	21%	23%	17%	0.49
CREBBP mutation	20%	15%	27%	0.09
TNFRSF14 mutation	17%	12%	26%	0.07
TBL1XR1 mutation	16%	17%	15%	1.00
GNA13 mutation	15%	12%	19%	0.41
MYC mutation	13%	14%	12%	1.00
CIITA mutation	12%	15%	7%	0.37
DICER1 mutation	11%	5%	19%	0.12
BCL2 mutation	11%	8%	15%	0.44
EZH2 mutation	11%	7%	19%	0.06
ATM mutation	11%	11%	12%	1.00
TNFAIP3 mutation	10%	11%	10%	1.00
CARD11 mutation	10%	11%	10%	1.00
Other subgroup	70%	75%	57%	0.21
EZB subgroup	22%	16%	33%	0.04
MCD subgroup	4%	4%	5%	1.00
ST2 subgroup	4%	7%	0%	0.16

Figure
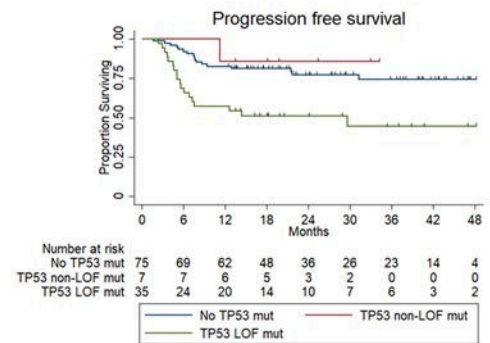
Figure 1

at least one *TP53* LOF mut vs only *TP53* non-LOF mut vs no *TP53* mut, 2y PFS was 51% vs 86% vs 77% (*P*=0.002) as depicted in the Figure and 2y OS was 64% vs 100% vs 91% (*P*=0.0004), respectively.

Finally, stratified log-rank demonstrated either inferior or a trend towards inferior 2y PFS for pts with vs without *TP53* LOF mut harboring high-risk features, including IPI score ≥3 (42% vs 80%, *P*=0.009), HGBL histology (25% vs 70%, *P*=0.046), non-GCB cell of origin by Hans algorithm (52% vs 81%, *P*=0.01), *MYC* rearrangement (33% vs 48%, *P*=0.17), *MYC-BCL2* double hit lymphoma (40% vs 67%, *P*=0.34) and EZB genetic subgroup (30% vs 81%, *P*=0.04).

Conclusions

TP53 mut identified through CLMA, specifically those resulting in LOF, predict for inferior clinical outcomes in pts with newly-diagnosed DLBCL/HGBL. Results of CLMA can be practically used to inform prognosis and/or identify pts for clinical trials investigating therapies targeting derangements caused by specific mut.