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POSTER ABSTRACTS

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Heterogeneity of TP53 Mutations in Mantle Cell Lymphoma- Challenges in Risk Stratification and Subclassification

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Introduction:
Somatic mutations in TP53 occur in approximately 10-20% of mantle cell lymphoma (MCL) patients (pts) at diagnosis. Eskelund and colleagues (Blood 2017) demonstrated poor survival among 20 pts with TP53-mutated MCL following intensive induction and transplant, and reported sequence-level variant data. However, TP53 mutations are heterogeneous, and few studies in MCL provide detailed sequencing data or variant allele frequency (VAF). Furthermore, the clinical impact of TP53 mutations may vary, and there is no algorithm shown to predict outcome for a given variant. We hypothesized that high VAF, or presence of a "disruptive" TP53 mutation as reported in squamous cell carcinoma (SCC; Poeta NEJM 2007), may adversely impact prognosis in MCL. To address this, we analyzed all MCL pts with available TP53 sequencing data at our center, including exact TP53 variant data and VAF, sMIPI score, and classification as disruptive vs not, and impact on survival from time of testing.

Methods:
Institutional records were analyzed with IRB approval, identifying 65 MCL pts who underwent sequencing for TP53 mutation from any tumor sample, as a single-gene assay or part of a panel. We analyzed VAF, type of mutation, and sMIPI score at time of TP53 testing. We classified TP53 mutations as "disruptive" or not according to method of Poeta and colleagues; these mutations result in a STOP codon, or an amino acid polarity change in the L2-L3 DNA binding domain of the TP53 protein (Poeta NEJM 2017). The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS) from time of TP53 testing to death or last follow up, and the log-rank test was used to compare outcomes based on TP53 mutational status. Among TP53 mutated cases, Cox proportional analyses were performed to explore the impact of the following covariates on survival: disruptive status, VAF, sMIPI score at time of TP53 testing, and presence of complex cytogenetics.

Results:
Sixty-five pts underwent TP53 sequencing, and 23 (35%) had a TP53 mutation (mTP53+). mTP53+ pts had inferior PFS (p=0.03) compared to TP53 wild-type, and a trend toward inferior OS (p=0.07); median OS was 26 months (95% CI: 8.1, NA) from time of TP53 testing.
Ki-67 index, blastoid histology, and age were similar between mTP53+ and wild-type status, but mTP53+ pts had a higher rate of complex cytogenetics (> 3 lesions; 48% vs 26%). SMIPI was also higher in mTP53+ pts (median score 6, interquartile range (IQR) range 4-7) vs TP53 wild-type pts (median 4, IQR range 3-5.2). MTP53+ pts were more likely to have received a BTK-inhibitor (BTK-I) (91 % vs 64%) and CAR-T therapy (39% vs 18%).
Details of the mTP53+ subset are shown in Table 1; 4 pts had >1 TP53 mutation, median VAF was 40%, and 30% of pts had a disruptive mutation. Among mTP53+ pts, on univariate analysis, higher sMIPI at time of TP53 testing (p=0.003) was associated with worse OS (Table 2). In a multivariable Cox model including VAF >= 40%, presence of disruptive mutation, sMIPI, and complex cytogenetics, only sMIPI at time of TP53 testing was associated with inferior OS (p=0.02).

Conclusion:
TP53 variants in MCL are diverse, and in our cohort were largely unique from those reported by Eskelund and colleagues (Blood 2017). Despite now-routine application of sequencing and improvements in therapy, both of which may attenuate the negative prognostic impact of TP53 mutation, we confirmed poor outcomes in mTP53+ MCL. Among mTP53+ pts, only sMIPI predicted inferior OS on both univariate and multivariate analysis. Higher VAF and adoption of a clinical algorithm from SCC

failed to discriminate among TP53 variants in terms of prognosis. Larger datasets of uniformly tested MCL pts are needed to elucidate prognosis among TP53 mutation variants, and improve understanding and management of mTP53+ MCL.

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Table 1. mTP53+ Patient Characteristics

mTP53+ Patient Characteristics (N=23)	Frequency
Timing of TP53 mutation testing	
Pre-treatment	15 (65%)
Post-treatment	8 (35%)
s-MIPI at TP53 testing	
Low risk	3 (13%)
Intermediate risk	7 (30%)
High risk	13 (57%)
Complex cytogenetics	11 (48%)
Multiple TP53 mutations	4 (17%)
Other mutations	3 (13%)
CXCR4	1
CCND1	2
ATM	1
NOTCH2	1
TP53 Mutation Characteristics (N=27)	**Frequency**
Unique mutations	25 (93%)*
Type of mutation	
Missense	22 (81%)
Frameshift	2 (7%)
Nonsense	2 (7%)
Coding silent	1 (4%)
Disruptive mutation (Poeta NEJM 2007)	8 (30%)
VAF, median (range)	40% (4-88)
VAF >= 40	11 (41%)
Known somatic mutation (COSMIC database)	25 (93%)
Mutation shared with Nordic dataset (Eskelund Blood 2017)	4 (15%)**
*Three patients had identical c.753G>A variants. **Mutations also reported in the Nordic dataset were c.753G>A (N=3) and c.536A>G (N=1).	

Table 2. Univariate and multivariate Cox models for overall survival.

	Univariate Model		Multivariate Model	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
VAF >= 40	3.15 (0.67,14.72)	0.15	0.48 (0.03, 7.07)	0.60
Presence of disruptive mutation	1.24 (0.35, 4.31)	0.74	4.12 (0.31, 54.2)	0.28
sMIPI at time of TP53 sequencing	1.96 (1.25, 3.07)	**0.003**	2.56 (1.16, 5.62)	**0.02**
Complex cytogenetics	5.88 (0.73, 47.18)	0.09	9.42 (0.48, 183.9)	0.14

Figure 1

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