Analysis of Double-Hit lymphoma cases by genetic subtype

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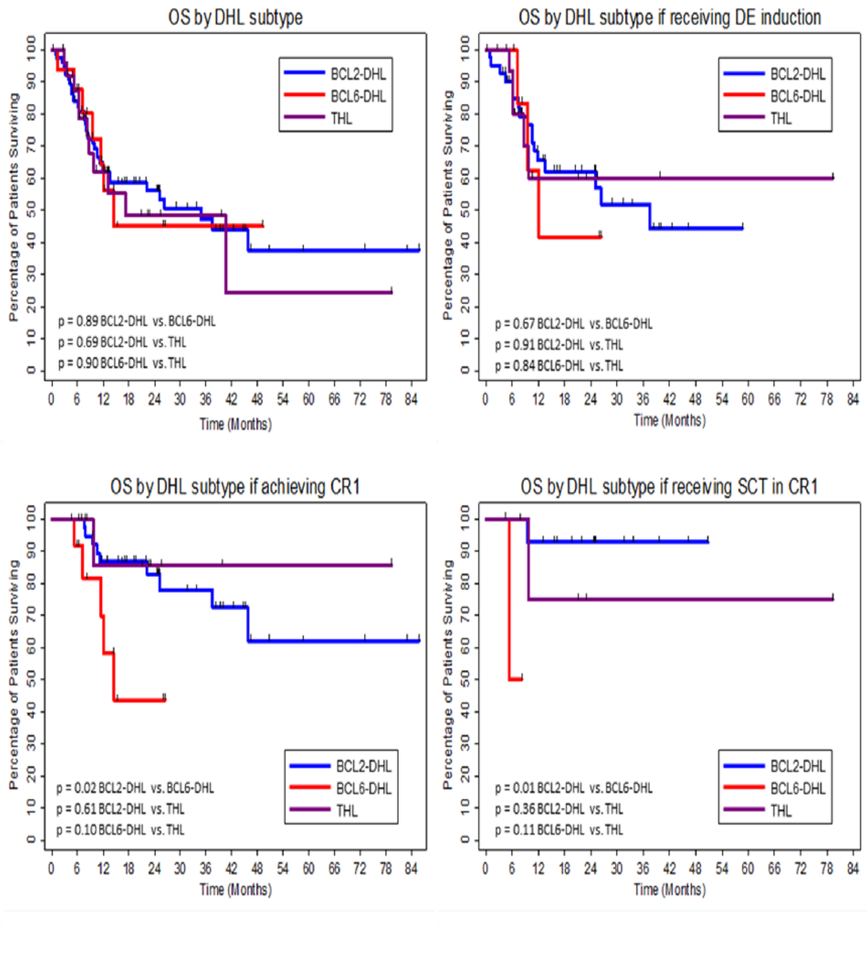
Background:

- Double-hit" lymphoma (DHL) is most commonly defined as a B cell non-Hodgkin lymphoma with rearrangement of c-MYC in addition to BCL2 and/or BCL6
- Inconsistency of uniform testing for all three gene rearrangements as well as the lack of clear reporting of outcomes based on treatment received limit the current understanding of the significance of DHL subtype
- We performed a comprehensive comparative analysis of DHL patients by genetic subtype

Methods:

From our previously-described database of DHL patients (Blood 2014 124:2354-61), we identified cases which underwent metaphase karyotyping or fluorescence in situ hybridization for c-MYC as well as both BCL2 and BCL6 rearrangements.
Cohorts were defined by the presence (+) or absence (-) of rearrangements: c-MYC+/BCL2+/BCL6- (BCL2-DHL), c-MYC+/BCL2-/BCL6+ (BCL6-DHL) and c-MYC+/BCL2+/BCL6+ (THL).
Dose-escalated (DE) regimens were defined as R-EPOCH, R-hyperCVAD and R-CODOX-M/IVAC
Therapy was given at the discretion of the treating physician.
Overall survival was calculated from the date of diagnosis to the date of death or last documented follow-up. Categorical variables were analyzed by Fisher's exact test. Survival times were analyzed by logistic regression and depicted by Kaplan Meier survival plots. Univariate and multivariate analyses were performed using Cox proportional-hazards regression, and variables with P<0.05 on univariate analysis were included in multivariate analysis.



Conclusion:

- BCL6-DHL patients may be more likely to achieve CR1 than BCL2-DHL and THL patients but may also experience shorter OS once in CR1, even if receiving SCT
- Outcomes for THL patients may not differ from those of BCL2-DHL patients
- High rates of primary refractory disease and relapse seen across all subtypes provide a rationale for offering novel therapeutic approaches to these pts in the front-line setting
- Comprehensive partner gene rearrangement testing may allow for identification of candidates for gene-specific targeted therapies

Baseline Characteristics

	BCL2-DHL n=76 (%)	BCL6-DHL n=16 (%)	THL n=25 (%)	*P* BCL2-DHL vs. BCL6-DHL	*P* BCL2-DHL vs. THL	*P* BCL6-DHL vs. THL
Age				1.00	0.49	0.53
<60 years	35 (46)	7 (44)	14 (56)			
≥60 years	41 (54)	9 (56)	11 (44)			
Ki67				0.41	0.16	0.75
<90%	37 (49)	6 (38)	8 (32)			
≥90%	36 (47)	10 (62)	17 (68)			
Unknown	3 (4)					
Histology				0.42	0.82	0.75
DLBCL	32 (42)	9 (56)	12 (48)			
BCLU/BLL	41 (54)	7 (44)	13 (52)			
Other	3 (4)					
Cell of Origin				***0.001***	0.35	0.14
GCB	60 (79)	9 (56)	14 (56)			
non-GCB	5 (7)	7 (44)	3 (12)			
Unknown	11 (14)	0	8 (32)			
IPI				0.76	0.47	0.75
<4	45 (59)	7 (44)	18 (72)			
≥4	28 (37)	6 (38)	7 (28)			
Unknown	3 (4)	3 (18)	0			
Extanodal disease				***0.04***	0.49	***0.02***
No	32 (42)	2 (13)	13 (52)			
Yes	44 (58)	14 (87)	12 (48)			
LDH				0.07	***0.001***	0.51
Normal	12 (16)	6 (38)	13 (52)			
Elevated	60 (79)	9 (56)	11 (44)			
Unknown	4 (5)	1 (6)	1 (4)			
Stage				0.49	0.56	1.00
<3	13 (17)	4 (25)	6 (24)			
≥3	63 (83)	12 (75)	19 (76)			
Bone marrow disease				1.00	1.00	1.00
No	40 (53)	8 (50)	13 (52)			
Yes	32 (42)	7 (44)	10 (40)			
Unknown	4 (5)	1 (6)	2 (8)			
CNS disease				0.34	0.66	1.00
No	49 (64)	9 (56)	14 (92)			
Yes	5 (7)	2 (13)	2 (8)			
Unknown	22 (29)	5 (31)				

Treatment Received and Outcomes

	DHL subtype			p value		
	BCL2-DHL	BCL6-DHL	THL	BCL2-DHL vs. BCL6-DHL	BCL2-DHL vs. THL	BCL6-DHL vs. THL
Receipt of DE[1]	55%	44%	65%	0.42	0.35	0.19
Receipt of CNS prophylaxis	39%	56%	40%	0.27	1.00	0.35
Complete response (CR1)	54%	75%	46%	0.17	0.49	0.10
If receiving DE[1]	55%	86%	63%	0.22	0.77	0.37
Stem cell transplant (SCT) in CR1	36%	17%	55%	0.30	0.31	0.09
Primary refractory disease	32%	13%	33%	0.14	1.00	0.25
If receiving DE[1]	25%	14%	14%	1.00	0.71	1.00
Relapse (if responding)	42%	50%	23%	0.75	0.33	0.23
If receiving DE[1]	36%	33%	25%	0.67	0.29	1.00
Median overall survival (months)[3]	34.8	14.5	17.2	0.89	0.69	0.90
If receiving DE[1]	37.5	12.1	Not yet reached	0.67	0.91	0.84
If achieving CR1	Not yet reached	14.5	Not yet reached	*0.02*	0.61	0.10
If receiving SCT in CR1	Not yet reached	5.3	Not yet reached	*0.008*	0.36	0.11
If not receiving SCT in CR1	Not yet reached	Not yet reached	Not yet reached	0.30	0.30	0.18
If relapsing	22.2	11.5	9.7	0.15	0.43	0.82

Univariate Analysis - Overall Survival

	MYC/BCL2		MYC/BCL6		THL	
	HR	p	HR	p	HR	p
Age (<60 vs. ≥60)		0.26		0.90		0.56
Ki67 (<90 vs. ≥90)		0.86		0.83		0.78
Histology (DLBCL vs. BCLU/BLL)		0.14		0.20		0.99
Cell of origin (GCB vs. non-GCB)		0.15		0.62		0.84
IPI (<3 vs. ≥3)	***3.0***	***0.02***		0.35	***3.6***	***0.04***
Extranodal disease (no vs. yes)		0.68		1.00		0.16
LDH (normal vs. elevated)	***7.6***	***0.046***		0.28		0.88
Stage (<3 vs. ≥3)	***4.2***	***0.05***		0.69		0.06
Bone marrow invovled (no vs. yes)	***2.6***	***0.01***		0.23	***10.4***	***0.03***
Treatment regimen (R-CHOP vs. DE)		0.79		0.53		0.22
CNS prophylaxis (no vs. yes)		0.43		0.48		0.25

Multivariate analysis - Overall Survival

	MYC/BCL2				THL	
	HR	p			HR	p
IPI (<3 vs. ≥3)		0.62				0.22
LDH (normal vs. elevated)		0.89				
Stage (<3 vs. ≥3)		0.55				
Bone marrow involved (no vs. yes)		0.14				0.11

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