Vincristine omission, but not dose reduction, is associated with decreased survival in elderly DLBCL patients

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Background

Diffuse large B-cell lymphoma (DLBCL) represents more than 30% of all diagnoses of non-Hodgkin lymphoma and about 50% of patients with DLBCL are more than 65 years old. These elderly patients frequently have other comorbidities which may alter their ability to receive standard curative therapy (R+/-CHOP or EPOCH) which makes the elderly an important population to examine. Due to multiple reasons including baseline neurological disorders, vincristine is often held or decreased to prevent further toxicities. There is limited data on how much vincristine contributes to the toxicities and outcomes of this regimen. The aim of this study is to assess the impact of vincristine on the toxicities and outcomes of the RCHOP regimen in the elderly population.

Methods

- Retrospective chart review that included elderly patients ≥70 years of age with Non-Hodgkin's lymphoma diagnosis (specifically large cell lymphoma) that initiated chemotherapy from 1999-2009.
- Data collected included: baseline demographics, disease characteristics, treatment given, response to therapy, toxicities
- Statistical analysis:
  - Kaplan-Meier & Cox proportional hazards model to estimate OS & PFS
  - Candidate factors on univariate analysis (UVA) were incorporated into a multivariate model (MVA) for each endpoint.
  - Fisher's exact test was used to analyze toxicities and vincristine group.

Results

Baseline characteristics

N = 325	Median (range)
Age at diagnosis	76 (69-94)
	N (%)
Gender	
Male	152 (47)
Female	173 (53)
Histology	
DLBCL only	291 (90)
DLBCL and others	29 (9)
Mediastinal DLBCL	3 (1)
T cell lymphoma	2 (1)
Cell of Origin	
Non-GC (ABC)	52 (16)
GC	96 (30)
Undetermined	177 (54)
Stage	
I/II non-bulky	111 (34)
III/IV or IIX (bulk)	211 (65)
Unknown	3 (1)
KPS	
≤ 70	90 (28)
> 70	213 (66)
unknown	22 (7)
aaIPI score	
0	81 (25)
1	90 (28)
2	90 (28)
3	63 (19)
Missing	1
Rituximab administered	
No	57 (18)
Yes	268 (82)
Number of chemo cycles administered	
1-2	25 (8)
3	48 (15)
4	36 (11)
5	22 (7)
6	187 (58)
7-8	7 (2)
Intended full/short course therapy	
Full course	214 (66)
Short Course (1-3 cycles)	111 (34)
Comorbidities that increase risk of vincristine toxicities	
No	224 (69)
Yes	101 (31)

Chemotherapy Relative Dose Intensity	N (%)
Vincristine RDI	
> 80%	200 (62)
50-80%	52 (16)
1-50%	54 (17)
0%	19 (6)
Cyclophosphamide RDI	
> 80%	287 (88)
50-80%	37 (11)
1-50%	1
0%	0
Doxorubicin RDI	
> 80%	279 (86)
50-80%	39 (12)
1-50%	7 (2)
0%	0

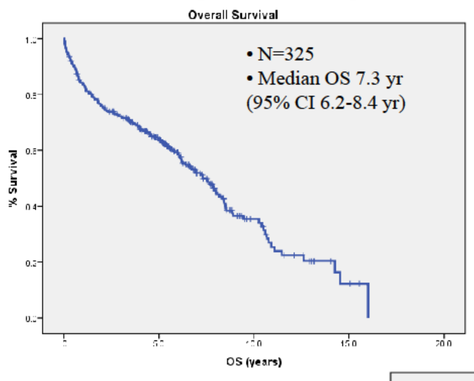
Vincristine RDI	Comorbidities	
	No	**Yes**
All Pts	**224 (69%)**	**101 (31%)**
>80%	150 (75%)	50 (25%)
50-80%	32 (62%)	20 (38%)
1-49%	32 (59%)	22 (41%)
0%	10 (53%)	9 (47%)
P value	**0.024**	

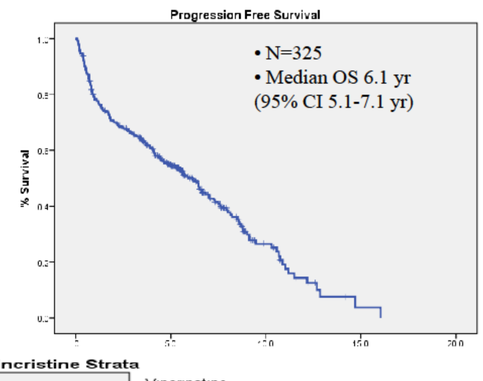
Vincristine RDI	≥ Grade 3 non-hematological toxicities N(%)		≥ Grade 4 hematological toxicities N(%)		Neurological or GI toxicities N(%)	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
> 80%	158 (79)	42 (21)	169 (84)	31 (16)	183 (91)	17 (9)
50-80%	28 (54)	24 (46)	35 (67)	17 (33)	37 (71)	15 (29)
1-49%	33 (61)	21 (39)	44 (81)	10 (19)	36 (67)	18 (33)
0%	10 (53)	9 (47)	15 (79)	4 (21)	15 (79)	4 (21)
P value	**<0.001**		*0.052*		**<0.001**	

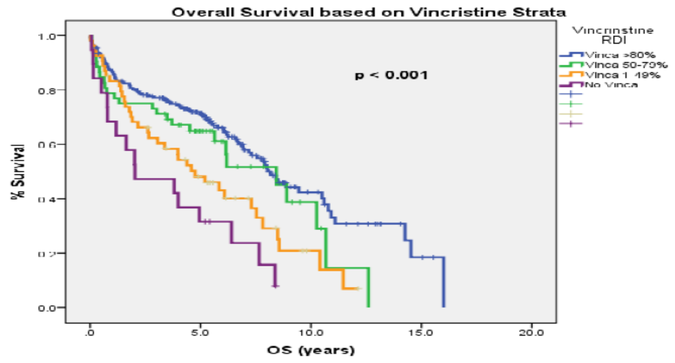
OS Analysis

Factor	UVA			MVA		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at dx (continuous)	1.09	(1.06, 1.12)	**< 0.001**	1.06	(1.02, 1.10)	**< 0.001**
Gender						
Male vs. female	0.94	(0.69, 1.27)	0.69			
Histology						
DLBCL and others vs. DLBCL only	0.75	(0.44, 1.28)	0.30			
GCB						
GCB vs. ABC	1.15	(0.68, 1.92)	0.61			
Undetermined vs. ABC	1.03	(0.64, 1.65)	0.91			
Stage						
III/IV or IIX (bulk) vs. I/II non-bulky	1.37	(0.99, 1.90)	*0.056*	0.86	(0.51, 1.45)	0.57
KPS						
≤ 70 vs. > 70	1.95	(1.40, 2.70)	**< 0.001**	1.01	(0.66, 1.55)	0.96
aaIPI score						
0 vs. 2/3	0.40	(0.27, 0.60)	**< 0.001**	0.34	(0.16, 0.69)	**0.003**
1 vs. 2/3	0.61	(0.43, 0.87)	**0.006**	0.54	(0.33, 0.87)	**0.012**
Rituximab given						
Yes vs. No	1.05	(0.72, 1.53)	0.79			
Intended full/short course						
Yes vs. No	1.77	(1.30, 2.40)	**< 0.001**	1.81	(1.24, 2.65)	**0.002**
Vincristine RDI						
50-80% vs. > 80%	1.35	(0.87, 2.10)	0.18	1.08	(0.67, 1.74)	0.75
1-49% vs. > 80%	1.91	(1.30, 2.80)	**0.001**	0.90	(0.57, 1.43)	0.66
0% vs. > 80%	3.07	(1.79, 5.26)	**< 0.001**	2.35	(1.30, 4.25)	**0.005**
Cyclophosphamide RDI						
50-80% vs. > 80%	1.62	(1.06, 2.48)	**0.026**	1.14	(0.40, 3.25)	0.80
Doxorubicin RDI						
50-80% vs. > 80%	1.45	(0.95, 2.20)	*0.085*	1.15	(0.40, 3.29)	0.80
1-49% vs. > 80%	2.51	(0.92, 6.82)	*0.072*	1.72	(0.58, 5.13)	0.33

*MVA for OS positive for age, aaIPI score, intended vs. short course, and 0% vincristine RDI







PFS Analysis

Factor	UVA			MVA		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at dx (continuous)	1.07	(1.04, 1.09)	**< 0.001**	1.03	(0.9998, 1.07)	*0.052*
Gender						
Male vs. female	0.87	(0.65, 1.16)	0.33			
Histology						
DLBCL and others vs. DLBCL only	0.94	(0.59, 1.50)	0.81			
GCB						
GCB vs. ABC	0.96	(0.60, 1.54)	0.87			
Undetermined vs. ABC	1.02	(0.67, 1.57)	0.92			
Stage						
III/IV or IIX (bulk) vs. I/II non-bulky	1.48	(1.09, 2.01)	**0.012**	0.85	(0.52, 1.41)	0.54
KPS						
≤ 70 vs. > 70	2.26	(1.66, 3.08)	**< 0.001**	1.29	(0.88, 1.90)	0.19
aaIPI score						
0 vs. 2/3	0.38	(0.26, 0.56)	**< 0.001**	0.32	(0.17, 0.62)	**< 0.001**
1 vs. 2/3	0.66	(0.48, 0.92)	**0.014**	0.63	(0.41, 0.97)	**0.034**
Rituximab given						
Yes vs. No	0.98	(0.69, 1.39)	0.91			
Intended full/short course						
Yes vs. No	1.58	(1.18, 2.10)	**0.002**	1.83	(1.28, 2.61)	**< 0.001**
Vincristine RDI						
50-80% vs. > 80%	1.18	(0.78, 1.78)	0.43	0.95	(0.60, 1.48)	0.80
1-49% vs. > 80%	1.78	(1.25, 2.54)	**0.001**	0.96	(0.63, 1.48)	0.87
0% vs. > 80%	2.49	(1.47, 4.23)	**< 0.001**	1.83	(1.03, 3.27)	**0.041**
Cyclophosphamide RDI						
50-80% vs. > 80%	1.71	(1.15, 2.54)	**0.008**	1.28	(0.51, 3.17)	0.60
Doxorubicin RDI						
50-80% vs. > 80%	1.43	(0.96, 2.12)	*0.078*	1.13	(0.44, 2.88)	0.80
1-49% vs. > 80%	2.80	(1.14, 6.86)	**0.024**	2.25	(0.84, 5.99)	0.11

*MVA for PFS positive for aaIPI score, intended vs. short course, and 0% vincristine RDI

Conclusion

- OS and PFS were both significantly reduced when vincristine was completely excluded from the regimens
- Importantly, in the MVA, dose reductions of vincristine did not impact OS and PFS
- Elderly DLBCL patients may be more likely to develop vincristine toxicities and therefore more likely to have dose reductions & omissions partly due to their baseline comorbidities
- Patients that did not receive vincristine often have the highest comorbidities which is confounding factor that impacted survival
- When comorbidities were included as a covariate, vincristine omission remains significant for OS and trends for PFS
- Therefore, for patients with high risk of developing vincristine toxicities, dose reductions are recommended or possibly substituting the conventional vincristine to liposomal vincristine

13icml 217--P
Aggressive B-cell lymphoma
Salma Afifi
DOI: 10.3252/pso.eu.13icml.2015
Poster presented at: 13-ICML
Printing supported by: Takeda ONCOLOGY
PosterSessionOnline.com