Comparison of lenalidomide and rituximab with chemo-immunotherapy in patients with untreated grade 1-2 follicular lymphoma treated at the MD Anderson Cancer Center

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Introduction

- The optimal initial therapy of follicular lymphoma (FL) remains unclear.
- R-chemo is highly effective but has significant toxicities
- The combination of lenalidomide and rituximab (R^2) is safe and effective[1] but comparative data are not available
- **Aim: to compare the outcomes of patients receiving BR or R-CHOP (with or without mainteance rituximab and R^2**

Methods

- Utilizing the Department of Lymphoma's clinical outcomes database, we identified patients treated between 2004 and 2014 with FL as standard of care and on clinical trials
- **Inclusion criteria:**
  - untreated grade 1-2 advanced stage FL
  - Treated with BR +/- maintenance R-CHOP +/- maintenance or R2.
  - Patients with concurrent DLBCL or grade 3 FL were excluded (all received R-CHOP)

	R-CHOP n= 119	R-CHOP + M n=65	BR n=45	BR + M n=33	R^2 n=94	*P*
median age (range), years	57 (23 - 81)	57 (33 - 74)	61 (30 - 85)	61 (35 - 85)	55 (28 - 84)	0.04
female (%)	53 (45%)	27 (42%)	23 (51%)	16 (48%)	43 (46%)	0.90
stage						
3	31 (26%)	14 (22%)	9 (20%)	8 (24%)	39 (41%)	0.03
4	88 (74%)	51 (78%)	36 (80%)	25 (76%)	55 (57%)	
B symptoms	33 (28%)	13 (20%)	7 (16%)	4 (12%)	8 (9%)	0.01
performance status						
unknown	12 (10%)	3 (5%)	11 (24%)	6 (18%)	4 (4%)	<0.001
0	49 (41%)	25 (38%)	14 (31%)	20 (61%)	71 (75%)	
≥1	58 (49%)	37 (57%)	20 (44%)	7 (21%)	19 (20%)	
hemoglobin <120g/L	28 (24%)	7 (11%)	9 (20%)	3 (9%)	3 (3%)	<0.001
elevated serum LDH	38 (32%)	10 (15%)	6 (13%)	6 (18%)	4 (4%)	<0.001
elevated serum β2m	74 (62%)	34 (52%)	19 (42%)	17 (52%)	25 (27%)	<0.001
lymphopenia	40 (34%)	27 (42%)	13 (29%)	12 (37%)	10 (11%)	<0.001
monocytosis	65 (55%)	31 (48%)	22 (49%)	13 (39%)	26 (28%)	<0.001
FLIPI						
low (0-1)	19 (16%)	18 (28%)	5 (11%)	6 (18%)	37 (39%)	<0.001
int (2)	37 (31%)	26 (40%)	23 (51%)	11 (33%)	39 (42%)	
high (3-5)	63 (53%)	21 (31%)	17 (38%)	16 (48%)	18 (19%)	
GELF high tumor burden	106 (89%)	62 (95%)	38 (84%)	27 (81%)	67 (71%)	0.001

Table 1. Baseline characteristics of patients according to treatment group.

	R-CHOP n= 119	R-CHOP + M n=65	BR n=45	BR + M n=33	R^2 n=94
median follow-up (range), years	8.0 (0.3 - 15)	3.8 (0.2 - 13.6)	2.3 (0.2 - 5.9)	2.3 (0.8 - 5.1)	3.4 (0.4 - 6.4)
3-year PFS (95%CI)	60% (51-69)	72% (59-82)	63% (42-78)	97% (80-100)	87% (78-93)
3-year OS (95%CI)	92% (86-96)	97% (88-98)	85% (66-94)	100% (-)	97% (89-99)

Table 2. Outcomes of patients according to primary treatment strategy.

candidate factor	PFS hazard ratio (95%CI)	PFS *P*	OS hazard ratio (95%CI)	OS *P*
FLIPI				
low	-	-	-	-
intermediate	1.51 (0.89 - 2.56)	0.12	5.37 (0.68 - 42.4)	0.11
high	1.85 (1.11 - 3.08)	**0.018**	15.45 (2.09 - 114.06)	**0.007**
FLIPI2				
low	-	-	-	-
intermediate	1.90 (0.87 - 4.17)	0.11	1.03 (0.23 - 4.64)	0.97
high	2.45 (1.12 - 5.40)	**0.025**	2.82 (0.66 - 12.02)	0.16
age>60	0.75 (0.52 - 1.08)	0.12	1.62 (0.84 - 3.15)	0.15
lymphopenia	0.95 (0.63 - 1.41)	0.78	2.13 (1.09 - 4.19)	**0.03**
monocytosis	1.04 (0.72 - 1.50)	0.21	0.85 (0.43 - 1.67)	0.64
hemoglobin <120g/L	1.39 (0.87 - 2.20)	0.17	2.74 (1.34 - 5.61)	**0.006**
platelets <100 x 10^9/L	1.09 (0.45 - 2.67)	0.85	1.28 (0.31 - 5.33)	0.74
bone marrow involvement	1.46 (1.01 - 2.12)	**0.043**	1.38 (0.69 - 2.73)	0.36
elevated serum LDH	1.69 (0.13 - 2.53)	**0.01**	2.45 (1.24 - 4.83)	0.01
B symptoms	1.56 (1.03 - 2.36)	**0.036**	2.11 (1.03 - 4.34)	**0.04**
ECOG performance status ≥1	1.59 (1.09 - 2.31)	**0.014**	5.19 (2.25 - 11.97)	**<0.001**
nodal sites ≥3	1.41 (0.88 - 2.24)	0.15	1.23 (0.51 - 3.01)	0.64
elevated serum β2m	1.92 (1.31 - 2.82)	**0.001**	3.54 (1.54 - 8.13)	**0.003**
treatment				
RCHOP	-	-	-	-
RCHOP + maintenance	0.64 (0.40 - 1.02)	0.06	0.34 (0.12 -1 .00)	0.051
BR	1.17 (0.65 - 2.14)	0.59	1.95 (0.75 - 5.11)	0.17
BR + maintenance	0.19 (0.05 - 0.79)	**0.02**	<0.01 (*)	**<0.001**
R^2	0.35 (0.21 - 0.62)	**<0.0001**	0.18 (0.04 - 0.77)	**0.02**

Table 3. Prognostic factors for progression free and overall survival by univariate analysis (prognostic factors adjusted for treatment).

candidate factor	PFS hazard ratio (95%CI)	PFS *P*	OS hazard ratio (95%CI)	OS *P*
age>60	0.62 (0.36 - 1.05)	0.08	2.65 (0.92 - 7.69)	0.07
lymphopenia	0.99 (0.57 - 1.74)	0.99	1.94 (0.63 - 5.95)	0.25
hemoglobin <120g/L	1.20 (0.64 - 2.27)	0.56	0.85 (0.26 - 2.74)	0.79
bone marrow involvement	1.50 (0.89 - 2.54)	0.13	3.27 (0.97 - 11.09)	0.057
elevated serum LDH	1.10 (0.61 - 2.00)	0.73	1.72 (0.53 - 5.57)	0.37
B symptoms	0.87 (0.48 - 1.57)	0.65	1.03 (0.32 - 3.34)	0.96
ECOG performance status ≥1	1.26 (0.77 - 2.08)	0.35	9.40 (2.41 - 36.67)	**0.001**
elevated serum β2m	1.45 (0.81 - 2.58)	0.21	3.46 (0.86 - 13.96)	0.08
nodal sites ≥3	1.39 (0.77 - 2.54)	0.27	0.47 (0.15 - 1.55)	0.22
treatment				
RCHOP	-	-	-	-
RCHOP + maintenance	0.55 (0.29 - 1.07)	0.08	0.07 (0.01 - 0.65)	**0.02**
BR	1.99 (0.93 - 4.27)	0.08	3.14 (0.66 - 14.95)	0.15
BR + maintenance	0.23 (0.17 - 0.89)	0.15	<0.01 (*)	**<0.001**
R^2	0.39 (0.17 - 0.89)	**0.02**	0.35 (0.04 - 3.25)	0.36

Table 4. Prognostic factors for progression free and overall survival by multivariate analysis, adjusted for treatment strategy.

"Although patients treated with R-chemo had more high-risk features, multivariate analysis suggests that treatment with R^2 was associated with superior PFS"

Results

- 356 patients were identified, with **median follow-up 4 (range 0.2 - 15.0) years**
- R^2 resulted in superior PFS than R-chemo without maintenance (*P*=0.0002) but not with maintenance (P=0.13) **Figure 1A**
- R^2 resulted in superior OS compared with R-chemo without maintenance (*P*=0.003) but not with maintenance rituximab (P=0.72) **Figure 1B**
- In the multivariate analysis adjusted for treatment group none of the baseline characteristics remained prognostic for PFS and only ECOG performance status ≥1 was associated with inferior OS. **Table 4**

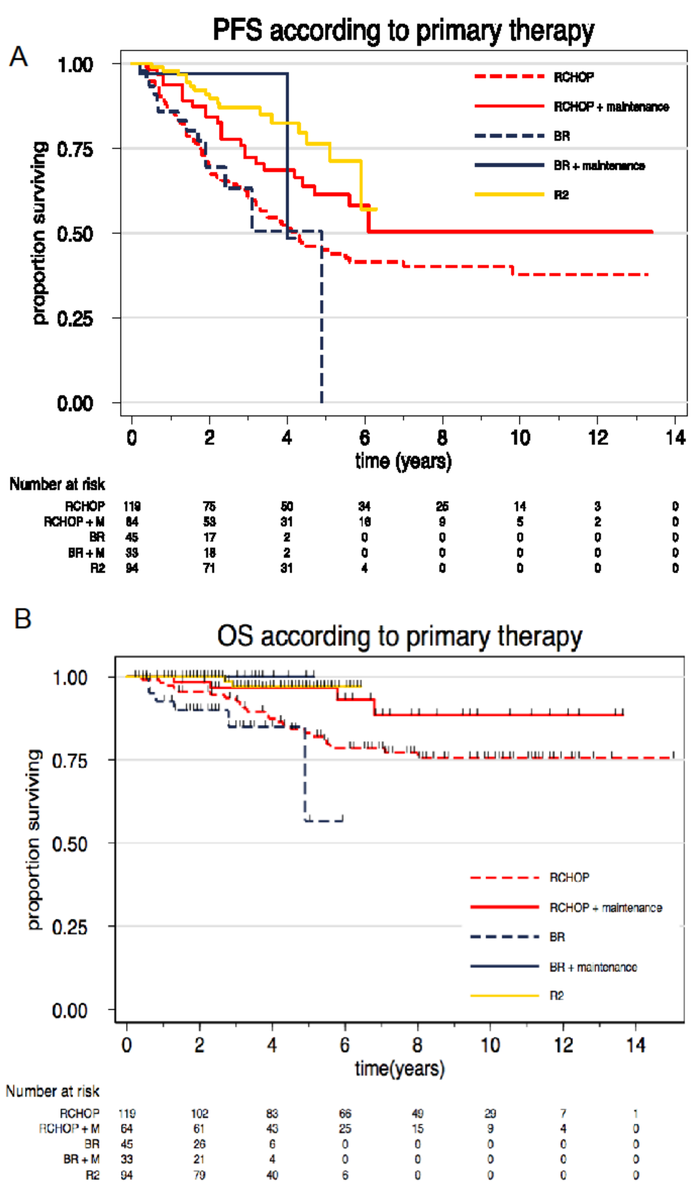

Figure 1. **A** PFS of all patients according to primary therapeutic strategy B PFS of patients treated with R-chemo with or without maintenance rituximab **C** OS of all patients according to primary therapeutic strategy **D** OS of patients treated with R-chemo with or without maintenance rituximab

- Treatment with R^2 was associated with superior PFS compared with R-CHOP (HR 0.39 [95%CI 0.17 - 0.89], *P*=0.02).
- In patients treated with BR or R-CHOP, maintenance resulted in superior PFS (HR 0.38 [95%CI 0.21 - 0.68], **Figure 1C)** and OS (HR 0.09 [95%CI 0.01 - 0.68]), **Figure 1D**).

Discussion

- Within the limitations of a retrospective non-randomized study, R^2 was associated with improved PFS compared with R-CHOP and BR without maintenance R
- R^2 may result in similar PFS to R-chemo with maintenance R
- In patients treated with R-chemotherapy, the use of maintenance R improves PFS, confirming the PRIMA data.[1]
- Although numbers were modest BR + maintenance R appears an effective strategy

Conclusion

- Although baseline characteristics were imbalanced, our multivariate analysis suggests R^2 may improve PFS in patients with untreated FL over R-chemo without maintenance.
- A large ongoing randomized study comparing R2 and R-chemotherapy is in progress

References

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Indolent lymphoma

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