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Similar Safety Profile for Rituximab and Obinutuzumab as Maintenance for Follicular Lymphoma: Evidence from a Real-World Multicenter Retrospective Cohort Study

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INTRODUCTION

Follicular lymphoma patients treated with obinutuzumab (O) based chemoimmunotherapy as first line therapy showed increased progression free survival with excess toxicity in the GALLIUM trial as compared to those treated with rituximab (R) based treatment[1]

Conversely, in our previous real-world study, toxicity was similar between the two anti-CD20 therapies during the induction and the six months post induction period[2].

AIM

To compare:

Real life toxicity profile between O vs. R maintenance therapy in follicular lymphoma after first line induction chemoimmunotherapy

Progression free survival (PFS) and overall survival (OS) between the two groups

METHODS

A multicenter retrospective study of adult patients with follicular lymphoma treated with O- or R- based chemoimmunotherapy, focusing on the maintenance period.

As obinutuzumab was approved by the Israeli health authorities on 1/1/2018, to try and ameliorate selection bias, we compared the best standard of care before and after its approval (R vs. O-based therapy, respectively)

The primary outcome was any infection, defined as the rate of patients with at least one infection according to the treating physician, among O- and R-groups, recorded during maintenance and six months post the maintenance period.

RESULTS

Characteristics of patients –

- A total of 156 patients (78 patients in each group) from five medical centers in Israel treated between 2016-2019 were included in the cohort in the induction phase
- We excluded 22 patients due to missing data or lack of maintenance therapy (15 and 7 in the O and R group, respectively)
- A total of 134 patients were included in the maintenance phase analysis – 63 and 71 patients received O and R maintenance, respectively
- The most common adjacent induction chemotherapy was bendamustine (n= 79, 59%) followed by CHOP (n=43, 32%)
- Baseline characteristics of patients were comparable between groups, except higher incidence of diabetes mellitus and hypertension in the R-group (See Table I)
- The median number of maintenance cycles in the O vs. the R group were 11 (IQR, 7-12) and 12 (IQR 8-12), respectively

Outcomes –

- Overall, the O- and R- groups were comparable in relation to rates of:
- any infection, occurring in 75 patients (61.9% and 50.7%, p=0.21)
- Grade 3-4 infections (19% vs. 19.7%, p=0.49)
- Febrile neutropenia (6.3% vs. 4.2%, p=0.71)
- There was a trend towards higher prevalence of viral infections in the O vs. R group (28.6% vs. 11.3%, p=0.052) (Table II)
- Other hematological and non-hematological adverse events were also comparable between the two groups, apart from more infusion-related reactions in the R-group (8.4% vs. 0%, p=0.028)
- Treatment discontinuation rates were also similar (p=0.278)
- There was no difference in all-cause mortality between the groups (9% and 17% in O vs. R group respectively, p=0.301)
- There were five cases of death d/t COVID-19 infection during the maintenance therapy, two in the R group and three in the O group.
- In a univariate analysis, none of the baseline characteristics were significantly associated with any infection.
- In Kaplan Meyer Survival Analysis, using the long-rank test for PFS, there was an advantage for O-group vs. R group (p=0.03) without difference in OS

Table I – Characteristics of patients, according to anti-CD20 therapy (n=134)

Variable	R-group (n=71)	O-group (n=63)	All patients (n=134)	*p-value*
Gender – Male, n (%)	37 (52)	28 (44)	65 (48)	0.392
Age at maintenance onset, median (IQR)	65 (53.5-71)	66 (54-78)	65 (54-78)	0.9
No.of cycles of maintenance, med. (IQR)	12 (8-12)	11(7-12)	11 (8-12)	0.7
***Comorbidities*, n (%)**				
Hypertension	27 (38)	9 (14.3)	36 (26.9)	0.003*
Diabetes Mellitus	16 (22.5)	3 (4.8)	19 (14.2)	0.005*
CKD(GFR≦60ml/min)	0	1 (1.6)	1 (0.75)	0.470
Liver disease	1 (1.4)	0	1 (0.75)	1
COPD	5 (7)	0	5 (3.7)	0.060
IHD	3 (4.2)	1 (1.6)	4 (3)	0.622
CHF	4 (5.6)	2 (3.2)	6 (4.5)	1
Smoking	11 (15.5)	7 (11.1)	18 (13.4)	0.613
Charlson comorbidity index, med. (IQR)	4 (3-5)	4 (3-5)	4 (3-5)	0.1331
***Disease characteristics*, n (%)**				
FL grade				
Grade 1-2	51 (71.8)	42 (66.7)	93 (69.4)	0.806
Grade 3a	13(18.3)	14 (22.2)	27 (20.1)	
Grade 3b	2 (2.8)	3 (4.8)	5 (3.7)	
FL stage				
Stage 2	6 (8.4)	3 (4.8)	9 (6.7)	0.197
Stage 3	19 (26.8)	26 (41.3)	45 (33.6)	
Stage 4	46 (64.8)	34 (54)	80 (59.7)	
BM involvement	22 (31)	25 (40)	47 (35.1)	0.366
Elevated LDH, n (%)	39 (55)	27 (43.9)	66 (49)	0.375
***Induction treatment*, n (%)**				
CHOP	24 (33.8)	19 (30.2)	43 (32.1)	1
Bendamustine	43 (60.6)	36 (57.1)	79 (59)	
COP	3(4.2)	8 (12.7)	11 (8.2)	

For all dichotomous variables, n patients (%), with all patients assessed, unless otherwise indicated. For all continuous variables, median (IQR).
*p < 0.05 - statistically significant difference between treatment cohorts
IQR – Interquartile range; CKD – chronic kidney disease; GFR – glomerular filtration rate; COPD – chronic obstructive pulmonary disease; IHD – ischemic heart disease; CHF – chronic heart failure; FL – follicular lymphoma; BM=- bone marrow ;LDH – lactate dehydrogenase; CHOP – cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; COP – cyclophosphamide, vincristine sulfate (Oncovin), and prednisone.

Table II – Characteristics of 118 infectious episodes reported in 75 of 134 patients, according to the R vs. O groups

Variable, n (%)	R-group (n=36)	O-group (n=39)	Total (n=75)	*p-value*
Neutropenic fever	3 (4.2)	4 (6.3)	7 (5.2)	0.711
Grade 3-4 Infection	14 (19.7)	12 (19)	26 (19.4)	0.492
Bacteremia	1 (1.4)	2(3.2)	3 (2.2)	1
Sepsis	4 (5.6)	2 (3.2)	6 (4.5)	0.43
Oral Antibiotic	25 (35.2)	26 (41.3)	51 (38.1)	0.546
IV Antibiotic	14 (19.7)	9 (14.3)	23 (17.2)	0.342
Hospitalization d/t infection	9 (12.7)	5 (7.9)	14 (10.5)	0.568
Fatal infection (other than COVID19)	2 (2.8)	0	2 (1.5)	
Fatal COVID19 Infection	2 (2.8)	3 (4.8)	5 (3.7)	
Clinical/microbiological documented infection				
Skin infection	4 (5.6)	2 (3.2)	6 (4.5)	0.288
Sinusitis	4 (5.6)	3 (4.8)	7 (5.2)	
URTI	8 (11.3)	15 (23.8)	23 (17.2)	
Pneumonia	7 (9.9)	11 (17.5)	18 (13.4)	
UTI	5 (7)	1 (1.6)	6 (4.5)	
Gastroenteritis	2 (2.8)	0	2 (1.5)	
Documented HSV infection	0	1 (1.6)	1 (0.75)	
Documented VZV infection	1 (1.4)	2 (3.2)	3 (2.2)	
***Types of infection according to pathogen*††**				
Bacterial infections-antibiotic-treated	11 (15.5)	13 (20.6)	24 (17.9)	0.725
Viral infections	8 (11.3)	18 (28.6)	26 (19.4)	0.052
Fungal infections	2 (2.8)	1 (1.6)	3 (2.2)	1

For all dichotomous variables, n patients (%), with all patients assessed, unless otherwise indicated. For all continuous variables, median (IQR).
†† Percentages out of patients with available data.
URTI – upper respiratory tract infection; UTI – urinary tract infection; HSV – herpes simplex virus; VZV –varicella-zoster virus; IV – intravenous; IQR – interquartile range;

CONCLUSIONS

In this real-world study of first line anti-CD20 maintenance therapy post chemoimmunotherapy in patients with follicular lymphoma, we observed:

- Similar toxicity between O- compared with R- therapy in the maintenance and 6 months post maintenance period
- A statistically advantage in PFS for O group vs R group.

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