Maintenance rituximab following induction R-CHOP chemotherapy in patients with composite or discordant, indolent and aggressive, B-cell non-Hodgkin lymphomas

Composite lymphoma (COM) is an uncommon pathological diagnosis in which two or more distinct lymphomas are encountered within a single tissue sample. In contrast, discordant lymphoma (DIS) represents two or more distinct histologies encountered concurrently at two or more separate anatomic sites. There are no published data describing the optimal initial management of COM/DIS lymphomas, as these patients have been traditionally excluded from studies of indolent, aggressive, and transformed indolent lymphomas.[1-4]

In British Columbia, Canada, patients with COM/DIS lymphomas are initially treated with R-CHOP with the goal of curing the aggressive component, while simultaneously attaining a sustained remission in the indolent component.[5-8] Maintenance rituximab (MR) is subsequently recommended in responding patients to prolong long-term disease control of their indolent lymphoma.[9-11] We estimated the outcomes of patients with COM/DIS lymphomas treated with R-CHOP followed by MR in comparison to those managed with R-CHOP induction alone prior to the introduction of MR.

Patients over 16 years of age with newly diagnosed COM/DIS lymphoma, including co-existing indolent B-cell non-Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL) between January 2001 and December 2013 were identified in the BCCA Lymphoid Cancer Database. All patients received R-CHOP induction with or without MR (R-CHOP-MR). Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, grade 3B follicular lymphoma (FL), mantle cell lymphoma, and non-DLBCL aggressive histology (i.e. Hodgkin lymphoma, Burkitt lymphoma, peripheral T-cell lymphoma) were excluded. The original pathology reports were reviewed. All tissue biopsies were centrally reviewed by an experienced BCCA hematopathologist at the time of diagnosis and treatment.

Patients with advanced and limited stage disease received a maximum and minimum of 8 and 3-4 cycles of chemotherapy, respectively, with or without consolidative radiotherapy. After January 2006, a treatment policy was introduced recommending MR 375 mg/m^2 once every three months for two years (i.e. 8 doses) in patients with CR/PR after R-CHOP, as described by van Oers *et al.*[12] The administration of MR, including number of doses, was verified for all patients using the Provincial Pharmacy Database.

Multivariate Cox proportional hazards regression analyses were performed by including COM *versus* DIS, use of MR, and variables with $P<0.1$ in univariate analyses into the model. Variables with $P<0.05$ were considered statistically significant in the final models. Data were analyzed using the Statistical Package for the Social Sciences (SPSS v.14.0 for Windows; SPSS Inc., Chicago, IL, USA). The study was approved by the University of British Columbia/BCCA Research Ethics board.

A total of 150 patients were identified, of whom 43 received pre-policy R-CHOP. In the 107 post-policy patients, 55 received MR, while 52 did not receive MR even though they were potentially eligible; reasons for this included: 38 unknown, 6 progressive disease (PD) immediately prior to the start of MR despite initial response to induction R-CHOP, 3 refused MR, 3 significant R-CHOP toxicity, one lost to follow up prior to MR initiation, and one enrolled in a clinical trial not permitting MR.

Table 1. Baseline patients' characteristics according to diagnosis: composite (COM) *versus* discordant (DIS) lymphoma.

Characteristics	Composite N=58	Discordant N=40	P
Age			
≤ 60 years	29 (50%)	11 (28%)	0.026
> 60 years	29 (50%)	29 (72%)	
Sex			
Male	30 (52%)	25 (63%)	0.291
Female	28 (42%)	15 (38%)	
Performance status			
0 – 1	47 (81%)	22 (55%)	0.006
≥ 2	11 (19%)	18 (45%)	
Lactate dehydrogenase			
Normal	35 (64%)	14 (35%)	0.006
Elevated	20 (36%)	26 (65%)	
Ann Arbor Stage			
I/II	13 (22%)	0	<0.001
III/IV	45 (78%)	40 (100%)	
Number of extranodal sites			
< 2	48 (83%)	18 (45%)	<0.001
≥ 2	10 (17%)	22 (55%)	
IPI			
Low	17 (29%)	3 (8%)	
Low-intermediate	18 (33%)	7 (18%)	<0.001
High-intermediate	17 (31%)	11 (27%)	
High	3 (6%)	19 (47%)	
Largest tumor mass			
< 10 cm	40 (49%)	29 (73%)	0.706
≥ 10 cm	18 (31%)	11 (27%)	
Type of indolent NHL			
Follicular	53 (91%)	15 (37%)	<0.001
Low grade, NOS	0	25 (63%)	
Marginal zone	4 (7%)	0	
Lymphoplasmacytic	1 (2%)	0	
Bone marrow involvement			
Indolent NHL	13 (22%)	34 (85%)	<0.001
DLBCL	5 (9%)	2 (5%)	
Negative	40 (69%)	4 (10%)	
Response to R-CHOP			
Complete	47 (81%)	30 (75%)	0.474
Partial	11 (19%)	10 (25%)	
Maintenance rituximab			
No	18 (31%)	25 (63%)	0.002
Yes	40 (69%)	15 (37%)	

IPI: International Prognostic Index; NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified.

Fifty-eight (59%) and 40 (41%) patients had COM and DIS lymphomas, respectively (Table 1). Forty-three (44%) were treated with R-CHOP and 55 (56%) R-CHOP-MR (Table 2). Patients treated with R-CHOP-MR received a median of 8 (range 1-8) doses of MR. While 39 of 55 (71%) patients completed the intended two years of MR, the other 16 discontinued MR prematurely for the following reasons: 8 (50%) progressed during treatment, 6 experienced significant MR toxicity, one developed acute myeloid leukemia, and one was lost to follow up.

With a median follow up of 11.4 years (range 2.2-14.6) in living patients treated with R-CHOP and 7.1 years (range 3.1-10.7) in patients treated with R-CHOP-MR, there were 21 (49%) and 17 (31%) relapses, respectively ($P=0.10$). Of these, 14 relapsed with indolent histology, 14 DLBCL [including 3 in the central nervous system

(CNS) only] and 10 had no biopsy at relapse (8 subsequently had aggressive and 2 cases had indolent clinical behavior on review of medical records). Thus, there were 7 (33%) indolent and 14 (67%) aggressive relapses in patients treated with R-CHOP, and 9 (53%) indolent and 8 (47%) aggressive relapses in patients treated with R-CHOP-MR (*P*=0.32). Twenty-one patients eventually died from lymphoma (12 with DLBCL relapse, 6 without a biopsy but with aggressive clinical behavior at relapse, and all 3 who developed a CNS recurrence).

There was no statistical difference in outcomes with the addition of MR: PFS [Hazard ratio (HR) 0.73, 95%CI: 0.41-1.31; *P*=0.288] including COM (*P*=0.407) or DIS (*P*=0.638) (Figure 1A and B); freedom from progression

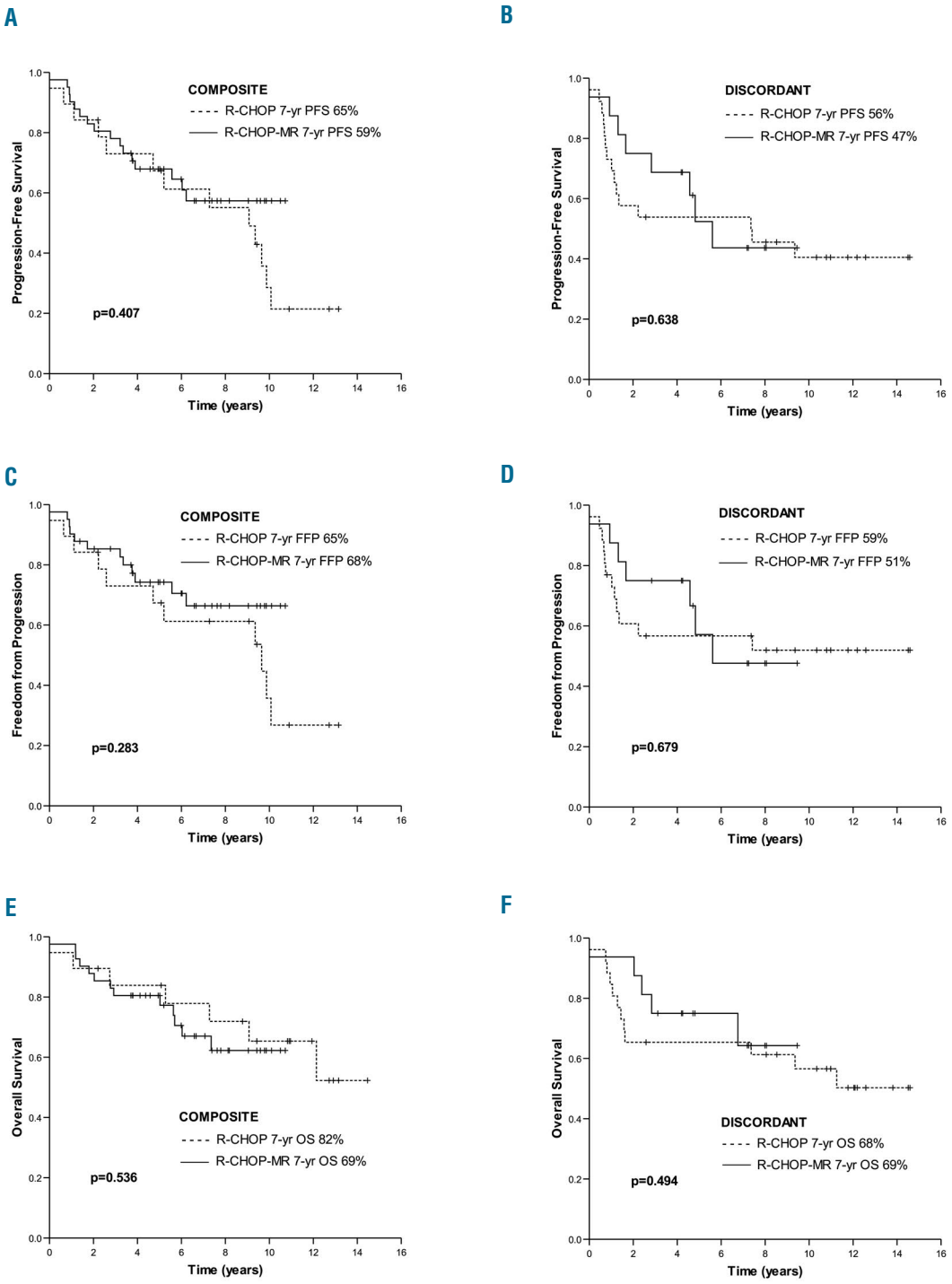

Figure 1. Outcomes according to maintenance rituximab. Progression-free survival: (A) composite lymphoma (COM), (B) discordant lymphoma (DIS); freedom from progression: (C) COM, (D) DIS; overall survival: (E) COM, (F) DIS.

(FFP) (HR 0.67, 95%CI: 0.35-1.29; *P*=0.235) including COM (P=0.283) or DIS (*P*=0.679) (Figure 1C and D); OS (HR 0.95, 95%CI: 0.46-1.95; *P*=0.889), including COM (*P*=0.536) or DIS (*P*=0.494) (Figure 1E and F). The addition of MR did not impact freedom from indolent progression in the overall study cohort (*P*=0.504), or when the analysis was broken down by COM (*P*=0.769) *versus* DIS (*P*=0.274). In the subgroup of patients with FL (23 R-CHOP, 44 R-CHOP+MR), the addition of MR did not impact PFS (*P*=0.602), FFP (*P*=0.526), or OS (*P*=0.771).

Age over 60 years was the only variable associated with worse PFS and FFP in uni- and multivariate analyses. Elevated LDH and poor performance status were associated with worse FFP in multivariate analysis. Histology (COM *vs.* DIS) and use of MR were not associated with worse outcomes in uni- or multivariate analyses. No variables impacted OS.

Fifty-two patients diagnosed after the treatment policy introduction in 2006 did not receive MR. There were no differences in an era-to-era (i.e. intent-to-treat) analysis comparing pre-policy (2001-2005, n=43) and post-policy (2006-2013, n=107) patients. A per-protocol (i.e. as-treated) analysis was also performed comparing 95 patients treated with R-CHOP and 55 treated with R-CHOP-MR (all 2001-2013), regardless of era. Again, there were no differences in outcomes.

In this retrospective cohort of patients with COM/DIS lymphomas treated with R-CHOP, the addition of MR was not associated with improved outcomes. Although the PRIMA trial only evaluated patients with FL,[9] we included a broader range of indolent lymphomas. This is particularly relevant for 25 of 40 (63%) DIS patients in whom trephine bone marrow biopsy precluded adequate indolent lymphoma classification. In these patients, the malignant marrow infiltrate was very small, the quality of the core biopsy was suboptimal, or the biopsies did not reveal sufficient characteristic architectural or immunophenotypic features permitting accurate disease classification. Furthermore, most lymphoma subtypes can share similar patterns of bone marrow infiltration.[13] On the other hand, considering FL accounted for 68% of all cases in our cohort, and that our sub-group analysis of FL remained comparable in outcome, it is unlikely this would alter the overall conclusion.

In the PRIMA trial, CT scans were performed every six months for the first five years, including the first two years of MR.[9] In our cohort, patients were evaluated clinically every three months for two years, then every 6-12 months afterwards, and imaging assessments were only performed to investigate symptoms or new findings on physical examination. Therefore, the lack of standardized imaging limits our ability to capture true progression rates after chemoimmunotherapy, and likely underestimates them. On the other hand, our follow-up strategy was relatively similar across eras, reducing bias in the way PFS was captured between treatment groups, and may be more clinically relevant than that used in clinical trials.

In our institution, the MR schedule was not standard as it was given every three months based on data in the relapsed setting[12] rather than every two months based on data in the front-line setting.[9] Limited data suggest there are no significant differences in outcomes for those who receive MR every two compared to every three months, although there are more infections associated with the dose-dense schedule.[14]

Another possible explanation for the failure of MR is that relapses in the DLBCL would be expected to occur early in follow up and to not be prevented by the use of MR. To date most of the relapses have occurred during the first few years from diagnosis (when DLBCL relapses are expected to dominate). Indolent relapses, which may be delayed by MR, would not be expected to be the dominant type of relapse for a much longer time period and, thus, may not yet have become discernible in our study.

Ultimately, the retrospective study design, modest sample size, imbalances in baseline characteristics (poorer PS and more BM involvement in the R-CHOP group), imbalances in follow-up time, and lack of standardized imaging may preclude the detection of statistically significant differences. Additionally, cell of origin (CD10, BCL6, MUM1) and cytogenetic (*BCL2, BCL6*, and *MYC*) status for the aggressive component were not available for almost all patients. Because of these limitations, at our institution the current policy has not been modified.

Table 2. Baseline patients' characteristics according to maintenance rituximab.

Characteristics	Pre-policy R-CHOP only N=43	Post-policy R-CHOP + MR N=55	*P*
Age			
≤ 60 years	19 (44%)	21 (38%)	0.548
> 60 years	24 (56%)	34 (62%)	
Sex			
Male	27(63%)	28 (51%)	0.240
Female	16 (37%)	27 (49%)	
Performance status			
0 – 1	25 (58%)	44 (80%)	0.019
≥ 2	18 (42%)	11 (20%)	
Lactate dehydrogenase			
Normal	21/42 (50%)	28/53 (53%)	0.784
Elevated	21/42 (50%)	25/53 (47%)	
Ann Arbor Stage			
I/II	5 (12%)	8 (15%)	0.673
III/IV	38 (88%)	47 (85%)	
Extranodal sites			
< 2	25 (61%)	38 (70%)	0.395
≥ 2	16 (39%)	16 (30%)	
IPI			
Low	9/42 (21%)	13/53 (24%)	0.401
Low-intermediate	11/42 (26%)	15/53 (27%)	
High-intermediate	10/42 (23%)	18/53 (33%)	
High	13/42 (30%)	9/53 (16%)	
Largest tumor mass			
< 10 cm	31 (72%)	38 (69%)	0.434
≥ 10 cm	12 (28%)	17 (31%)	
Diagnosis			
Composite NHL	18 (42%)	40 (73%)	0.002
Discordant NHL	25 (58%)	15 (27%)	
Type of indolent NHL			
Follicular	23 (53%)	44 (80%)	0.021
Low grade, NOS	17 (40%)	8 (14%)	
Marginal zone	3 (7%)	2 (4%)	
Lymphoplasmacytic	0	1 (2%)	
Bone marrow involvement			
Indolent NHL	27 (56%)	20 (36%)	0.027
DLBCL	3 (7%)	4 (7%)	
Negative	13 (30%)	31 (56%)	
Response to R-CHOP			
Complete	36 (84%)	41 (75%)	0.272
Partial	7 (16%)	14 (25%)	

IPI: International Prognostic Index; NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified.

In conclusion, the addition of MR does not appear to improve outcomes in patients with COM/DIS lymphomas responding to R-CHOP, although comparisons are likely underpowered and 7-year median follow up in the MR group may not be sufficient. The role of MR in these uncommon lymphomas requires further exploration, and larger prospective trials are warranted to evaluate the role of maintenance therapies for this subgroup of patients.

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