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HIGH RISK OF TRANSFORMATION AND SECONDARY MALIGNANCIES IN FOLLICULAR LYMPHOMA PATIENTS TREATED WITH FIRST-LINE BENDAMUSTINE RITUXIMAB AND RITUXIMAB MAINTENANCE

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INTRODUCTION

Follicular lymphoma (FL) is an indolent non-Hodgkin lymphoma. It is an incurable disease with a pattern of relapsing and remitting. Bendamustine-rituximab (BR) has exhibited improved outcomes in first-line therapy. Nevertheless, concerns regarding secondary malignancies and the transformation into aggressive lymphoma have arisen.

A real-world data cohort of FL patients treated with BR showed a transformation rate at 3-years of 9%[1]. This is in contrast with the transformation rate reported in the long-term follow-up of the GALLIUM study of 4.2% (25 patients of 601)[2] and the BRIGHT study of 2.2 % (5 patients of 224)[3]. However, the biopsy at relapse was not mandatory in clinical trials. Such as in the GALLIUM study, biopsies were only reported for 18% of all patients with progressive disease and this number is unknown for the BRIGHT study. Additionally, in the BRIGHT study secondary malignancy, excluding NHL and nonmelanoma skin cancer, at 5 years was 10%.[3]

AIM

We aim to assess the outcomes in long-term follow-up of a cohort of FL patients treated within a tertiary care cancer center, including the transformation rate into aggressive lymphomas and the cumulative incidence of secondary malingnacies.

METHOD

Using the prospectively populated Lymphoma database at the Princess Margaret Cancer Centre, we evaluated the outcomes of FL patients intended to be treated with 6 cycles of BR and 2 years of rituximab maintenance as frontline therapy between 2013 and 2022. We assessed the overall rate response (ORR), progression-free survival (PFS), Duration of Response (DOR), and Overall Survival (OS) following the standard definitions. We assessed clinical characteristics at diagnosis and relapse. Moreover, based on the biopsy at first relapse, we classified the patients as transformed to a high-grade lymphoma (tFL) or as relapse/refractory (r/r FL). Differences between categorical variables were assessed using the $\chi 2$ test or Fisher exact test. Risk factors for transformation were assessed by calculating the odds ratio (OR) along with 95% confidence intervals (CIs) with a logistic regression model. The information regarding secondary malignancies was collected and we calculated the 5-year secondary incidence and the incidence rate. Time-to-event variables were estimated using the Kaplan-Meier method. Statistical significance was determined as $P < .05$.

RESULTS

137 patients were identified, and the characteristics at diagnosis are shown in *Table 1*; 126 (92%) completed BR treatment, and 115 (84%) underwent maintenance. The ORR and CR after BR were 87.6% and 36.5%, respectively. At a median follow-up of 6.3 years (IQR 4.0-8.6), 5-year Progression-Free Survival (PFS), Duration of Response (DOR), and Overall Survival (OS) were 65% (95% CI, 60%--69%),72% (68--76%), and 84.9% (82%--88%), respectively. *(Figures 1A & 1B)*

Disease progression occurred in 44 (32%) patients, with 18% progressing within 24 months (POD24). A biopsy was performed at the first relapse in 42 (95%) patients. In 26 (62%), it showed transformation into an aggressive lymphoma (tFL); 20/42 (47%) exhibited diffuse large B-cell lymphoma (DLBCL), and 6 (14%) showed DLBCL/high-grade B-cell lymphoma with MYC/BCL2 rearrangements. The characteristics at diagnosis did not differ between the patients with tFL and a relapse/refractory FL. (*Table 1)*

Among the POD24 patients, a transformation into aggressive lymphoma was found in 22 (88%). POD24 and elevated LDH at relapse were significant predictors of transformation in multivariate analysis (OR 46.3 [95% CI 4.8–441.4], $p < .001$ and OR 19.3 [95% CI 1.7-215.9],p=0.016). The median time from BR to transformation was 10 months (IQR 5-30), and the 5-year cumulative risk of transformation was 18 %. (*Figure 2A*)

The 5-year cumulative incidence of secondary malignancies among patients, excluding transformation and non-melanoma skin cancer, was 9%. The median time from BR to second malignancy was 23 months (IQR 7.5-74.5). (*Figure 2B)* Moreover, the incidence rate of secondary malignancies among patients was 20.4 per 1,000 person-year.

Figure 1A.Progression Free Survival after BR

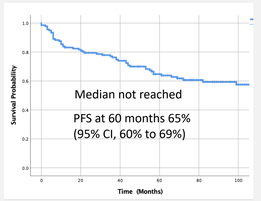


Figure 1B. Overal Survival after BR

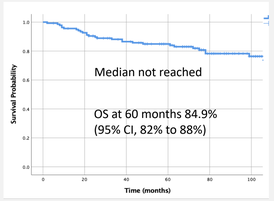


Figure 2A. Cumulative Risk of Transformation

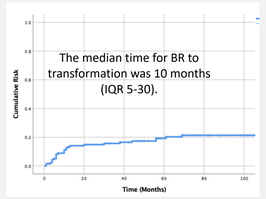


Figure 2B. Cumulative Risk of Secondary malignancies

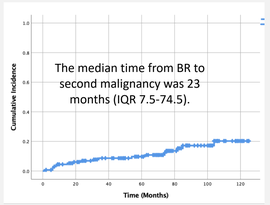


TABLE 1. Characteristics at Diagnosis of Patients who underwent Bendamustine Rituximab and Rituximab Maintenance treatment.

Variable	Total N= 137	r/r FL n=18	tFL n=26	*p*-value
Sex (Male) (%)	**47.4**	10 (57)	11 (42)	0.38[d]
Age				
At diagnosis median (IQR)	**60 (50.5-68.5)**	55 (49-61)	62 (59-67)	0.19"
At treatment median (IQR)	**62 (51.5-69)**	56 (51-63)	64 (61-69)	0.12"
Age over 70 y.o n (%)	**26 (23.4)**	2 (11)	6 (23)	0.43c
Stage at Diagnosis	**0**	0	0	
Stage I, n (%)	**14 (10.2)**	2 (11)	0	
Stage II, n (%)	**39 (28.5)**	5 (28)	10 (39)	
Stage III, n (%)	**84 (61.3)**	11 (61)	16 (62)	0.19[d]
Stage IV, n (%)				
B Symptoms at Diagnosis n (%)	**17 (12.4)**	1 (6)	6 (23)	0.21c
Bulky disease n (%)	**65 (47.4)**	9 (50)	12 (46)	0.80[d]
BM involvement				
Involved, n (%)	**59 (43.1)**	10 (57)	9 (35)	
Not assessed, n (%)	**36 (26.3)**	3 (17)	6 (23)	0.38[d]
LDH elevated at diagnosis (%)	**67 (48.9)**	10 (56)	16 (64)	0.57[d]
Grade at Diagnosis				
Grade 1-2, n (%)	**109 (79.6)**	16 (89)	18 (69)	
Grade 3A, n (%)	**21 (15.3)**	1 (6)	5 (19)	
Not assessed, n (%)	**7 (5.1)**	1 (6)	3 (12)	0.30 [d]
FLIPI at diagnosis				
Low risk (<1) n (%)	**24 (17.5)**	4 (22)	1 (4)	
Intermediate (2) n (%)	**36 (26.3)**	2 (11)	6 (24)	
High risk (>3) n (%)	**76 (55.5)**	12 (67)	18 (72)	0.13[d]

cFisher's exact test. [d]Chi square

CONCLUSIONS

These single-centre data are consistent with prospective clinical trial results in FL, with BR followed by rituximab maintenance offering prolonged 5-year PFS. However, we observed a notably higher rate of transformation to aggressive lymphomas compared to clinical trials, where rates of biopsy at progression are much lower. This observation underscores the need for biopsies at early progression/relapse, and has implications for trials designed to address markers of poor outcome (positive end of treatment PET scan or MRD), as tFL rates are underestimated when biopsies are not mandated by trial protocols. The elevated risk of secondary malignancies warrants further investigation through population-based studies.

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To all the patients and their families

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