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Early Progression As a Predictor of Survival in Marginal Zone Lymphomas: An Analysis from the FIL-NF10 Study

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Abstract:
Marginal zone Lymphomas (MZL) are indolent B cell non Hodgkin Lymphoma (INFL) and have a heterogeneous clinical behavior. Recently time to progression shorter than 24 months (POD24) was identified to stratify overall survival (OS) in follicular NHL and in INFL. Here we examined the ability of POD24 to predict subsequent OS in a large, international cohort of MZL as part of the NF10 prospective international registry (NCT02904577) headed by Fondazione Italiana Linfomi (FIL). POD24 was calculated only for MZL patients requiring immediate therapy and was defined as experiencing lymphoma progression within 24 months from diagnosis. Among the 1,325 patients enrolled in the NF10 study we identified 321 pts with MZL for whom immediate therapy was planned right after lymphoma diagnosis. Overall POD24 was confirmed in 59 patients (18%). Three-year OS for patients with POD24 was 53% with a HR of 19.5 (95%CI 8.4-45) compared with patients without POD24 (3 yr OS 95%). Association of POD24 with OS was confirmed for the subgroup of splenic and extranodal MZL. Assessment of POD24 stratifies subsequent outcome in MZL and identifies high risk population.

Conflict of interest: COI declared - see note

COI notes: SL holds a consultancy/advisory role from Roche, Celgene, Sandoz, Gilead and Teva. FC holds advisory role from Takeda and Janssen Cilag. MV holds advisory role from Janssen Cilag and Roche; travel expenses from Janssen Cilag, Abbvie and Gilead. FM holds an advisory role from Roche, Celgene and Sandoz; honoraria from Roche, Gilead, Mundipharma, Janssen and Takeda; travel expenses from Takeda and Celgene; research funding from Roche. DM holds advisory role from Janssen Cilag and Abbvie. OA hold advisory role from Celgene, Takeda, Janssen Cilag, Roche, Servier and Amgen; sponsorships from Gilead, Janssen Cilag, Servier, Celegene Takeda and Amgen. LA reports consulting or advisory roles for Bayer, Celgene, Gilead Sciences, Roche, Sandoz, Janssen-Cilag, VERASTEM and research funding from Gilead Sciences and participation in a speakers bureau for Celgene. All other authors have nothing to declare.

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Short title
Early progression in marginal zone lymphomas

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Key points

- Patients with Marginal zone lymphoma (MZL) who experience progressive disease within 24 months from initial systemic therapy (POD24) have a significant increase of the risk of Death.
- Association of POD24 with survival is confirmed for the main MZL subtypes

- **Abstract**

Marginal zone Lymphomas (MZL) are indolent B cell non Hodgkin Lymphoma (INFL) and have a heterogeneous clinical behavior. Recently time to progression shorter than 24 months (POD24) was identified to stratify overall survival (OS) in follicular NHL and in INFL. Here we examined the ability of POD24 to predict subsequent OS in a large, international cohort of MZL as part of the NF10 prospective international registry (NCT02904577) headed by Fondazione Italiana Linfomi (FIL). POD24 was calculated only for MZL patients requiring immediate therapy and was defined as experiencing lymphoma progression within 24 months from diagnosis. Among the 1,325 patients enrolled in the NF10 study we identified 321 pts with MZL for whom immediate therapy was planned right after lymphoma diagnosis. Overall POD24 was confirmed in 59 patients (18%). Three-year OS for patients with POD24 was 53% with a HR of 19.5 (95%CI 8.4-45) compared with patients without POD24 (3 yr OS 95%). Association of POD24 with OS was confirmed for the subgroup of splenic and extranodal MZL.

Assessment of POD24 stratifies subsequent outcome in MZL and identifies high risk population.

Introduction

Marginal zone Lymphomas (MZLs) originate from mature B lymphocytes, and include splenic, nodal and extranodal subtypes (SMZL, NMZL, ENMZL)[1]. Despite their indolent course a high heterogeneity of clinical behavior exists that warrants accurate tools to estimate the risk of relapse, progression or death in the individual patient. A prognostic index to foresee the outcome of all patients with MZL is missing but subtypes specific indexes have been proposed and validated for ENMZL [2] and for SMZL [3,4]. Recently the analysis of progression free survival (PFS) has been used to identify surrogate endpoints in B-cell NHLs, with Progression of Disease at 24 months (POD24) identified to stratify overall survival (OS) in follicular NHL.[5] Association of POD24 with OS has been confirmed in FL, Mantle Cell Lymphomas, Diffuse Large B-Cell and in peripheral T-cell Lymphoma and recently also in Indolent non follicular B-cell lymphomas (INFL).[6–9]

The NF10 Project was started in 2010 as a prospective observational study specifically conceived to investigate the outcome of INFL. We examined the ability of POD24 to predict subsequent OS in the large MZL cohort of patients enrolled in the NF10 study.

Methods:

Consecutive adult patients with newly diagnosed, histologic confirmed diagnosis of INFL were eligible for the NF10 study without any exclusion criteria and including SMZL, ENMZL, NMZL, lymphoplasmacytic lymphoma (LPL), Small Lymphocytic Lymphoma (SLL), and CD5-negative low-grade B cell lymphoma. Histologic diagnosis was required on tissue or on bone marrow biopsy and was based on local assessment. Patients were managed based on local institutional guidelines; treatment was left to physician discretion and was analyzed according to an intent to treat principle;. Watch and wait (WW) was defined as the decision not to treat

patients and by the absence of treatment within the first 3 months from the date of diagnosis. The definition of systemic therapy was applied to the use of systemic chemotherapy and of anti-CD20 monoclonal antibody alone or in combination with one or more chemotherapy agent; the use of antibiotics, radiotherapy or splenectomy were not considered as systemic therapies. The main aim of the current study was to validate the prognostic role of time to progression on the subgroup of patients with MZL who received immediate systemic therapy.

The main endpoint of this study was Overall Survival (OS); secondary endpoints were PFS and cause specific survival (CSS) [10]. POD24 was defined as experiencing lymphoma progression within 24 months from diagnosis. Survival analysis according to POD24 was calculated only for patients with events within 24 months (early progressors) or for those with at least 24 months of follow-up in case no POD24 defining event was reported (not early progressor). The OS was calculated from risk-defining event for early progressors; for patients without early progression os was computed starting at 24 months from diagnosis, to reduce the effect of early progressive disease patients. Patients censored or died before 24 months were excluded from analysis. The study was approved by local ethic committees at any active center and signed consent form was mandatory for all enrolled patients.

Results and discussion

Between July 2010 and July 2018, 1,325 INFL cases have been registered in the NF10 study by 65 centers in Europe and South America. Demographic and clinical characteristics are summarized in table 1. Overall, 321 patients who received immediate systemic therapy and who had an adequate follow-up were identified as the main study population. The median follow-up was 43 months (range 1-92). Five-year PFS was 64% (95% CI 56 to 71%). Salvage

treatment of patients with progressive disease was immunochemotherapy in 46 cases (55%), radiotherapy in 6 (7%), observation in 7(8%). High dose therapy followed by autologous stem cell transplant (ASCT) was reported in 3 cases and in 23 cases it was not possible to obtain details on salvage therapy (27%). Overall 31 patients died; progressive disease was reported as the cause of death in 19/31 cases (61%). Five-year OS was 88% (95% CI 83 to 92%).

POD24 was reported in 59/321 patients (18%). Three-year OS for patients with POD24 was 53% (95%CI 37-67%) with a HR of 19.5 (95%CI 8.4 – 45.4) when compared to patients without POD24 (88%%, 95%CI 89-98%) (Figure1). Association of POD24 with OS was also confirmed with a lower HR, for patients who were not immediately treated (POD24 rate 25%, HR for OS 2.69 CI95% 1.04 to 6.92). The association of POD24 with OS was confirmed in ENMZL, SMZL and Diss-MZL subgroups (Figure 1). Our data confirm the strong association of time to progression with OS as seen for FL and, more recently, in a study of INFL by the University of Iowa/Mayo Clinic[9]. Differently from the US series our study was focused on a homogeneous population of MZL patients prospectively recruited in an international study who were treated with systemic chemo and/or immunotherapy. Notwithstanding small differences between the two studies and the use of two slightly different endpoints, both support the strong association of time to progression with the risk of death.

Recent data on FL suggest that early events could be enriched with transformed cases with more aggressive behavior.[11] In our study 66% of deaths for POD24 patients were referred to lymphoma progression and higher mortality of early relapsed was confirmed also by CSS analysis; moreover among the 90 patients who experienced progressive disease we were able to identify 7 patients with histologically transformed MZL all of whom were counted as POD24 cases. Thus also if the rate of transformation in our series was low compared to other

reported series [12,13], our report suggests that histological transformation (HT) might play a role in defining the quality of early events.

Another issue with POD24 patients is about salvage treatment. In follicular lymphomas, two recent reports suggested that the use of ASCT might be a better option compared to conventional salvage therapies for early relapser[14,15]. In MZL the efficacy of ASCT is controversial and its role as salvage therapy for POD24 patients remains an open research question. Indeed, very few POD24 patients were treated with ASCT in our study.

The finding of early progression (POD24) as strong marker of poor outcome is useful but its clinical utility to support initial treatment choice is limited. Logistic univariate analysis adjusted by treatment modality (immunochemotherapy vs chemotherapy without rituximab) identified clinical and laboratory parameters associated with higher risk of POD24 (age >60, performance status, systemic symptoms, bone marrow involvement, low serum albumin, elevated LDH, Beta2Microglobulin, low Hemoglobin, reduced Platelet count, low Absolute lymphocyte count). Among tested prognostic scores FLIPI predicted the risk of POD24(12% and 27% for 0-2 and 3-5 risk factors; p=0.001). Future research efforts should focus on the identification of these high risk patients at the time of diagnosis, in order to enable personalized therapy.

In conclusion assessment of POD24 predicts subsequent outcome in MZL in need of therapy and its association with OS is confirmed for the main MZL subtypes. Our data have important implications for the management of patients with MZL and for a better understanding of the disease.

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AUTHOR CONTRIBUTIONS

SL and LA designed research, analyzed an interpreted data. LM performed statistical analysis, analyzed an interpreted data. All authors performed research, collected data, wrote and approved manuscript

CONFLICT OF INTEREST DISCLOSURES

SL holds a consultancy/advisory role from Roche, Celgene, Sandoz, Gilead and Teva. FC holds advisory role from Takeda and Janssen Cilag. MV holds advisory role from Janssen Cilag and Roche; travel expenses from Janssen Cilag, Abbvie and Gilead. FM holds an advisory role from Roche, Celgene and Sandoz; honoraria from Roche, Gilead, Mundipharma, Janssen and Takeda; travel expenses from Takeda and Celgene; research funding from Roche. DM holds advisory role from Janssen Cilag and Abbvie. OA hold advisory role from Celgene, Takeda, Janssen Cilag, Roche, Servier and Amgen; sponsorships from Gilead, Janssen Cilag, Servier, Celegene Takeda and Amgen. LA reports consulting or advisory roles for Bayer, Celgene, Gilead Sciences, Roche, Sandoz, Janssen-Cilag, VERASTEM and research funding from Gilead Sciences and participation in a speakers bureau for Celgene.

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Table 1 - Characteristic of the 321 MZL patients we received immediate systemic therapy (study population) and comparison with MZL patients enrolled in the NF10 who did not receive immediate therapy.

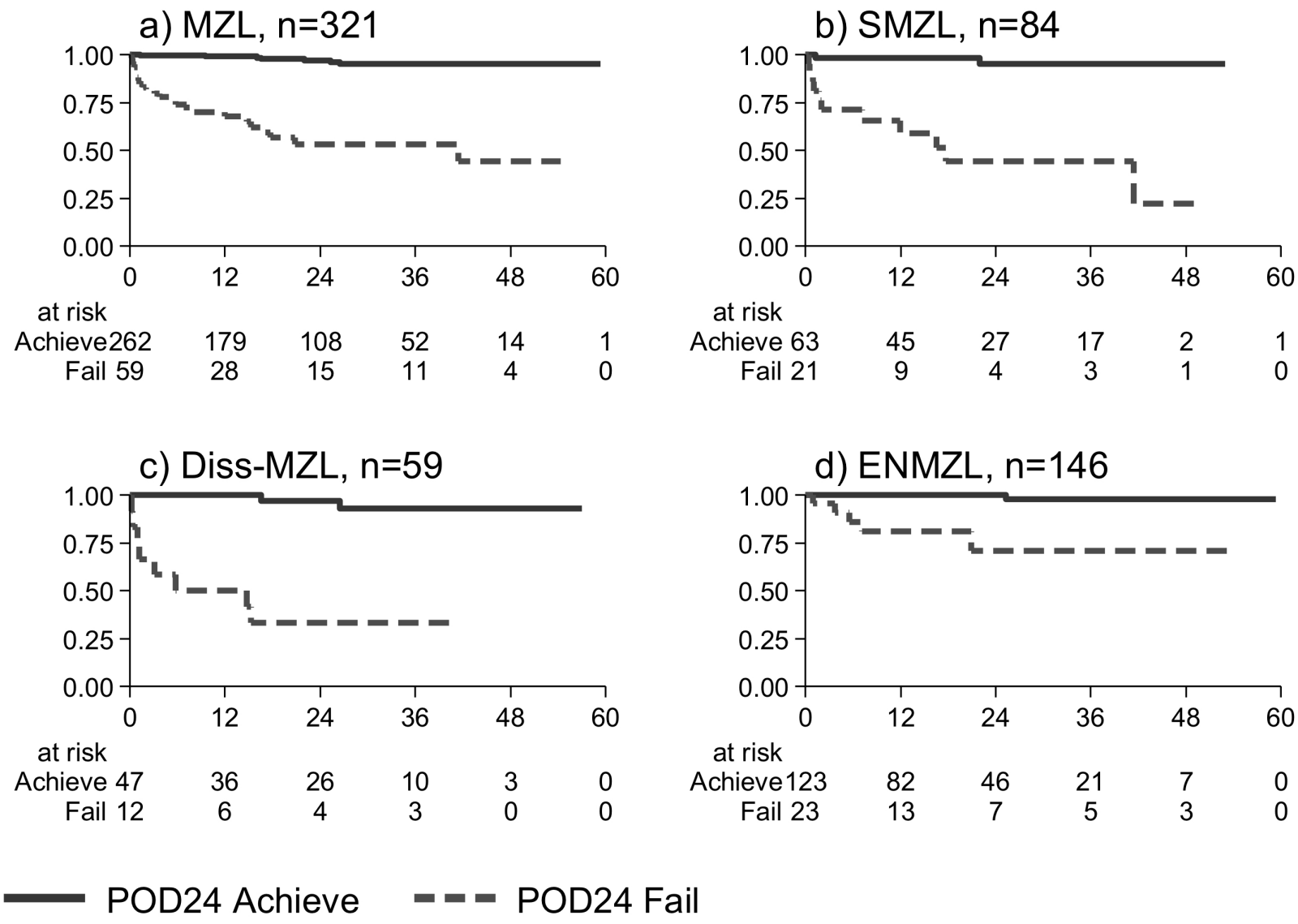
Factor		*Missing*	*Untreated (%)*	*Treated (%)*	*P*
Total			**286**	**321**	
MZL(*)	ENMZL	-	96 (34)	146 (46)	<0.001
	SMZL	-	122(43)	84 (26)	
	NMZL	-	30 (10)	32 (10)	
	DissMZL	-	38 (13)	59 (18)	
Age	> 60 years	-	203 (71)	202 (62)	0.039
ECOG PS	>1	3	8 (3)	21 (7)	0.036
Symptoms	B	3	19 (7)	66 (21)	<0.001
Hb	< 12g/dl	3	73 (26)	129 (40)	<0.001
Platelets	< $150x10^9$/ul	5	97 (34)	90 (28)	0.094
LDH	> UNL	30	61(23)	96 (31)	0.049
B2M	> UNL	17	96 (41)	156 (60)	<0.001
LN size	> 6cm	61	8 (3)	34 (11)	<0.001
Albumin	< 3.5 g/dl	74	15 (8)	51 (22)	<0.001
HBV serology	+	12	23 (8)	25 (9)	0.88
HCV serology	+	27	35 (12)	67 (21)	0.012
Treatment					
	Watch & wait	7	286(100)	-	
	Alk-Mono	-	-	16 (5)	
	R-Mono	-	-	30 (9)	
	R-Alkylating	-	-	83 (26)	
	R-CHOP	-	-	48 (15)	
	R-Bendamustine	-	-	112 (35)	
	R-Fludarabine	-	-	3 (1)	
	Other	-	-	21 (6)	

Legend to table: (*) Eligible patients were classified as SMZL, ENMZL and NMZL according to local pathologic diagnosis. Patients with histologic features consistent with MZL with concomitant involvement of the marrow and/or spleen and/or lymph nodes and/or extranodal sites but lacking the diagnostic features of splenic, nodal or extranodal MZL were categorized as disseminated MZL (dissMZL). MZL: Marginal Zone Lymphoma; ENMZL: Extranodal MZL; SMZL: Splenic MZL; NMZL: Nodal MZL; Diss MZL: Disseminated MZL; PS: Performance Status; Hb: Hemoglobin; LDH: Lactate dehydrogenase; B2M: beta2-microglobulin; LN: lymph node; HBV: Hepatitis B virus; HCV: Hepatitis C virus; Alk: alkylating agent; R: Rituximab

Figure legend:

Figure 1 Overall survival by POD24 and by marginal zone lymphoma subtypes

Overall survival from risk-defining event after diagnosis in patients with MZL who were immediately treated after diagnosis a) Patients with MZL: POD24 rate 18%; 3-yr OS POD24 achieve 95% vs fail 53%, p<0.001 [HR 19.5; 95%CI 8.40-45.4], b) Patients with SMZL: POD rate 25%: 3-yr OS POD24 achieve 95% vs fail 44%, p<0.001; c) Patients with diss-MZL: POD rate 20%: 3-yr OS POD24 achieve 93% vs fail 33%, p<0.001; d) Patients with ENMZL: POD rate 16%: 3-yr OS POD24 achieve 98% vs fail 71%, p<0.001. Association of POD24 with OS could not be assessed for nodal MZL patients because too few events have been reported in this subgroup to do any inference. Legend to figure: MZL, Marginal Zone Lymphoma; SMZL Splenic MZL; Diss MZL, Disseminated MZL; ENMZL, Extranodal MZL.


a) MZL, n=321
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60
at risk
Achieve 262 179 108 52 14 1
Fail 59 28 15 11 4 0
b) SMZL, n=84
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60
at risk
Achieve 63 45 27 17 2 1
Fail 21 9 4 3 1 0
c) Diss-MZL, n=59
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60
at risk
Achieve 47 36 26 10 3 0
Fail 12 6 4 3 0 0
d) ENMZL, n=146
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60
at risk
Achieve 123 82 46 21 7 0
Fail 23 13 7 5 3 0
POD24 Achieve
POD24 Fail

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