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Brief Report

CLINICAL TRIALS AND OBSERVATIONS

Early progression as a predictor of survival in marginal zone lymphomas: an analysis from the FIL-NF10 study

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KEY POINTS

- **Patients with MZL who experience POD24 from initial systemic therapy have a significantly increased risk of death.**
- **Association of POD24 with survival is confirmed for the main MZL subtypes.**

Marginal zone lymphomas (MZLs) are indolent nonfollicular B-cell lymphomas (INFLs) and have heterogeneous clinical behavior. Recently, time to progression of disease at 24 months (POD24) was identified to stratify overall survival (OS) in follicular non-Hodgkin lymphoma 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 headed by Fondazione Italiana Linfomi (FIL). POD24 was only calculated for MZL patients requiring immediate therapy and was defined as experiencing lymphoma progression within 24 months from diagnosis. Among the 1325 patients enrolled in the NF10 study, we identified 321 patients 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 hazard ratio of 19.5 (95% confidence interval, 8.4-45) compared with patients without POD24 (3-year OS, 95%). Association of POD24 with OS was confirmed for the subgroup of splenic and extranodal MZLs. Assessment of POD24 stratifies subsequent outcome in MZL and identifies a high-risk population. This trial was registered at www.clinicaltrials.gov as #NCT02904577. (*Blood*. 2019;134(10):798-801)

Introduction

Marginal zone lymphomas (MZLs) originate from mature B lymphocytes, and include splenic MZL (SMZL), nodal MZL (NMZL), and extranodal MZL (ENMZL) subtypes.[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 subtype-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 end points in B-cell non-Hodgkin lymphomas, with progression of disease at 24 months (POD24) identified to stratify overall survival (OS) in follicular non-Hodgkin lymphoma.[5] Association of POD24 with OS has been confirmed in follicular lymphoma (FL), mantle cell lymphomas, diffuse large B-cell, and in peripheral T-cell lymphoma and, recently, also in indolent nonfollicular B-cell lymphomas (INFLs).[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.

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

Factor	Missing	Untreated, n (%)	Treated, n (%)	*P*
Total		286	321	
MZL*				
ENMZL	—	96 (34)	146 (46)	<.001
SMZL	—	122 (43)	84 (26)	
NMZL	—	30 (10)	32 (10)	
Diss-MZL	—	38 (13)	59 (18)	
Age >60 y	—	203 (71)	202 (62)	.039
ECOG PS >1	3	8 (3)	21 (7)	.036
Symptoms, B	3	19 (7)	66 (21)	<.001
Hb <12 g/dL	3	73 (26)	129 (40)	<.001
Platelets <150 × 10^9/L	5	97 (34)	90 (28)	.094
LDH > UNL	30	61 (23)	96 (31)	.049
B2M > UNL	17	96 (41)	156 (60)	<.001
LN size >6 cm	61	8 (3)	34 (11)	<.001
Albumin <3.5 g/dL	74	15 (8)	51 (22)	<.001
HBV serology, +	12	23 (8)	25 (9)	.88
HCV serology, +	27	35 (12)	67 (21)	.012
Treatment				
Watch and 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)	

—, not applicable; Alk-Mono, monotherapy with alkylating agents; B2M, β2-microglobulin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; Diss-MZL, disseminated MZL; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; LDH, lactate dehydrogenase; LN, lymph node; R, rituximab.

*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 SMZL, NMZL, or ENMZL were categorized as Diss-MZL.

Study design

Consecutive adult patients with a newly diagnosed, histologically confirmed diagnosis of INFL were eligible for the NF10 study without any exclusion criteria, including SMZL, ENMZL, NMZL, lymphoplasmacytic lymphoma, small lymphocytic lymphoma, and $CD5^-$ 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 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 1 or more chemotherapy agents; 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 end point of this study was OS; secondary end points were PFS and cause-specific survival.[10] POD24 was defined as experiencing lymphoma progression within 24 months from diagnosis. Survival analysis according to POD24 was only calculated 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 the 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

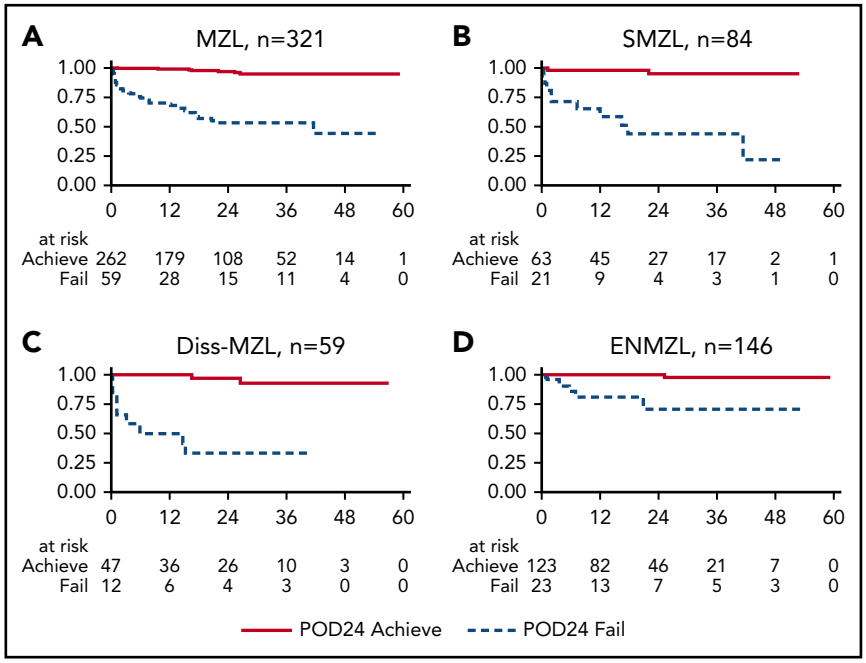

Figure 1. OS by POD24 and by MZL subtypes. OS from a risk-defining event after diagnosis in patients with MZL who were immediately treated after diagnosis. (A) Patients with MZL: POD24 rate, 18%; 3-year OS POD24, achieve 95% vs fail 53% ($P < .001$) (HR, 19.5; 95% CI, 8.40-45.4). (B) Patients with SMZL: POD rate, 25%; 3-year OS POD24, achieve 95% vs fail 44% ($P < .001$). (C) Patients with disseminated MZL (Diss-MZL): POD rate, 20%: 3-year OS POD24, achieve 93% vs fail 33% ($P < .001$). (D) Patients with ENMZL: POD rate, 16%; 3-year OS POD24, achieve 98% vs fail 71% ($P < .001$). Association of POD24 with OS could not be assessed for NMZL patients because too few events have been reported in this subgroup to do any inference.

or those who died before 24 months were excluded from analysis. The study was approved by local ethic committees at any active center and signed consent forms were mandatory for all enrolled patients.

Results and discussion

Between July 2010 and July 2018, 1325 INFL cases were registered in the NF10 study by 65 centers in Europe and South America (supplemental Appendix, available on the *Blood* Web site). 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 months). Five-year PFS was 64% (95% confidence interval [CI], 56% to 71%). Salvage treatment of patients with progressive disease was immunochemotherapy in 46 cases (55%), radiotherapy in 6 (7%), and observation in 7 (8%). High-dose therapy followed by autologous stem cell transplant (ASCT) was reported in 3 cases; 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 of 31 cases (61%). Five-year OS was 88% (95% CI, 83% to 92%).

POD24 was reported in 59 of 321 patients (18%). Three-year OS for patients with POD24 was 53% (95% CI, 37% to 67%) with a hazard ratio (HR) of 19.5 (95% CI, 8.4-45.4) when compared with patients without POD24 (88%; 95% CI, 89% to 98%) (Figure 1). 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; 95% CI, 1.04-6.92). The association of POD24 with OS was confirmed in ENMZL, SMZL, and disseminated MZL (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 chemotherapy and/or immunotherapy. Notwithstanding small differences between the 2 studies and the use of 2 slightly different end points, 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 also confirmed by cause-specific survival 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, if the rate of transformation in our series was low compared with other reported series,[12,13] our report suggests that histological transformation might play a role in defining the quality of early events.

Another issue with POD24 patients is salvage treatment. In FLs, 2 recent reports suggested that the use of ASCT might be a better option compared with conventional salvage therapies for early relapsers.[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 a 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 years, performance status, systemic symptoms, bone marrow involvement, low serum albumin, elevated lactate dehydrogenase, β2 microglobulin, low hemoglobin, reduced platelet count, low absolute lymphocyte count). Among tested prognostic scores, the Follicular Lymphoma International Prognostic Index (FLIPI) predicted the risk of POD24 (12% and 27% for 0-2 and 3-5 risk

factors; $P = .001$). 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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Authorship

Contribution: S.L. and L.A. designed research and analyzed and interpreted data; L.M. performed statistical analysis and analyzed and interpreted data; and all authors performed research, collected data, and wrote and approved the manuscript.

Conflict-of-interest disclosure: S.L. holds a consultancy/advisory role with Roche, Celgene, Sandoz, Gilead, and Teva. F.C. holds an advisory role with Takeda and Janssen Cilag. M.V. holds an advisory role with Janssen Cilag and Roche and received travel expenses from Janssen Cilag, AbbVie, and Gilead. F.M. holds an advisory role with Roche, Celgene, and Sandoz; received honoraria from Roche, Gilead, Mundipharma, Janssen, and Takeda; received travel expenses from Takeda and Celgene; and received research funding from Roche. D.M. holds an advisory role with Janssen Cilag and AbbVie. O.A. holds an advisory role with Celgene, Takeda, Janssen Cilag, Roche, Servier, and Amgen and has received sponsorships from Gilead, Janssen Cilag, Servier, Celegene, Takeda, and Amgen. L.A. reports consulting or advisory roles for Bayer, Celgene, Gilead Sciences, Roche, Sandoz, Janssen-Cilag, and Verastem; has received research funding from Gilead Sciences; and reports participation in a speakers' bureau for Celgene. The remaining authors declare no competing financial interests.

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Footnotes

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