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Early progression of disease predicts shorter survival in patients with mucosa-associated lymphoid tissue lymphoma receiving systemic treatment

Annarita Conconi,[1] Catherine Thieblemont,[2] Luciano Cascione,[3] Valter Torri,[4] Barbara Kiesewetter,[5] Gloria Margiotta Casaluci,[6] Gianluca Gaidano,[6] Markus Raderer,[5] Franco Cavalli,[3] Armando Lopez Guillermo,[7] Peter W. Johnson[8] and Emanuele Zucca[3,9] on behalf of the International Extranodal Lymphoma Study Group (IELSG)

[1]Division of Hematology, Ospedale degli Infermi, Biella, Italy; [2]Hemato-Oncology Department, Saint Louis Hospital, Paris, France; [3]Institute of Oncology Research, Bellinzona, Switzerland; [4]Clinical Research Methodology Laboratory, IRCCS–Mario Negri Institute, Milan, Italy; [5]Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; [6]Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy; [7]Department of Hematology, Hospital Clinic, Barcelona, Spain; [8]Cancer Research UK Centre Southampton General Hospital, Southampton, UK and [9]Division of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Haematologica 2020
Volume 105(11):2592-2597

Presented in part at the 2019 Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Chicago, IL, USA, May 31 - June 4, 2019 and at the 15th International Conference on Malignant Lymphoma (15-ICML) held in Lugano, Switzerland, June 18-22, 2019.

Correspondence:

ANNARITA CONCONI
annarita.conconi@aslbi.piemonte.it

Received: September 11, 2019

Accepted: January 2, 2020.

Pre-published: January 2, 2020

doi:10.3324/haematol.2019.237990

ABSTRACT

Early progression of disease, within 2 years of diagnosis, is linked with poor overall survival in follicular lymphoma but its prognostic role in extranodal marginal zone B-cell lymphoma is less clear. We sought to identify prognostic factors associated with early progression of disease and to determine whether early progression is associated with inferior overall survival. We analyzed the impact of early progression of disease using the dataset of the International Extranodal Lymphoma Study Group-19 (IELSG-19) clinical trial (training set of 401 patients randomly assigned to chlorambucil or rituximab or chlorambucil plus rituximab). Reproducibility was examined in a validation set of 287 patients who received systemic treatment. We excluded from the analysis patients in both sets who, within 24 months of starting treatment, died without progression or were lost to follow-up without prior progression. Overall survival was calculated from progression in patients with early disease progression and from 24 months after the start of treatment in those whose disease did not progress early (reference group). Early disease progression occurred in 69 of the 384 (18%) evaluable patients of the IELSG-19 study. Patients with a high-risk Mucosa-Associated Lymphoid Tissue - International Prognostic Index score were more likely to have early disease progression (P=0.006). The 10-year overall survival rate was 64% in the group with early disease progression and 85% in the reference group (hazard ratio = 2.42; 95% confidence interval: 1.35-4.34; log-rank P=0.002). This prognostic impact was confirmed in the validation set, in which early progression was observed in 64 out of 224 (29%) evaluable patients with 10-year overall survival rates of 48% in the group with early disease progression and 71% in the reference group (hazard ratio = 2.15; 95% confidence interval: 1.19-3.90; log-rank P=0.009). In patients with extranodal marginal zone B-cell lymphoma who received front-line systemic treatment, early disease progression is associated with poorer survival and may represent a useful endpoint in future prospective clinical trials.

Introduction

Marginal zone lymphomas (MZL) comprise three separate disease entities, which have individual epidemiological, molecular and clinical features. Extranodal marginal zone lymphoma (EMZL), also known as mucosa-associated lymphoid tissue (MALT) lymphoma, is the most common MZL subtype, accounting for approximately 50 to 70% of MZL and 5% to 8% of all B-cell lymphomas.[1-3] EMZL may involve virtually any tissue but most often affects organs that are normally devoid of lymphocytes, where it arises from lymphoid populations associated with chronic inflammatory processes of either infectious or autoimmune origin.[4] The clinical presentation is very heterogeneous and EMZL patients are managed with a variety of treatments. The natural course is usually indolent, particularly in patients with gastric lymphomas, and aggressive therapy is rarely required.[1,3,5] Outcomes may, however, differ depending on the organ involved.[2,6] We recently proposed a prognostic model, the MALT-lymphoma International Prognostic Index (MALT-IPI), which is based on age, disease stage and lactate dehydrogenase (LDH) concentration at diagnosis. MALT-IPI discriminated between patients with different progression-free survival (PFS) and overall survival (OS), and retained its prognostic utility in both gastric and non-gastric MALT lymphomas.[7] In this context, the identification of the minority of patients with shorter survival may become important, especially in the perspective of personalized medicine, and might form the basis for adapting therapeutic approaches.

In follicular lymphoma early progression of disease (POD), namely, within 24 months after diagnosis, has been reported to be associated with poor outcomes.[8] Currently, the clinical significance of early POD in EMZL is uncertain, and the impact of early POD on subsequent survival has not been properly explored yet.

The present study aimed to understand whether time to progression after first-line systemic therapy may be a factor affecting survival outcomes in EMZL. We analyzed data from the International Extranodal Lymphoma Study Group 19 (IELSG-19) clinical trial to determine whether early POD is predictive of inferior OS in this disease, and then validated our findings in an independent cohort.

Table 1. The characteristics of the patients in the validation and test sets.

	Test set (IELSG-19)	Validation set
Number of patients	401	287
Years of diagnosis	2003-2010	1983-2014
Median age at diagnosis (IQR)	61 years (51-69)	63 years (51-72)
Male/female ratio	197/204	115/172
Stage III-IV, n (%)	175 (44%)	140 (49%)
Performance status>1[a], n (%)	6 (1.5%)	14 (5%)
LDH >UNL[b], n (%)	42 (10.5%)	42 (16%)
β_2-microglobulin >UNL[c], n (%)	46 (16%)	73 (43%)
Primary gastric lymphoma, n (%)	171 (43%)	125 (44%)
IPI, high-intermediate/high risk[d], n (%)	77 (19%)	88 (31%)
MALT-IPI, high risk[e], n (%)	68 (17%)	69 (26%)
First-line treatment, n (%)		
Chemotherapy only	131 (33%)	158 (55%)
Rituximab and chemotherapy	132 (33%)	64 (22%)
Doxorubicin-containing regimen	0%	60 (21%)
Rituximab only	138 (34%)	28 (10%)
Other[f]	0%	37 (13%)
Median follow-up (IQR)	7.4 years (5.6-9.7)	5.7 years (2.3-9.2)
Progression-free survival		
5-year PFS rate (95% CI)	62.8% (57.6-67.6)	46.9% (39.8-53.6)
10-year PFS rate (95% CI)	50.8% (44.5-56.8)	29.7% (21.6-38.2)
Median (IQR)	NR (2.6-NR)	4.6 years (1.8-15.1)
Overall survival		
5-year OS rate (95% CI)	90.3% (86.9-92.9)	85.7% (80.1-89.9)
10-year OS rate (95% CI)	80.0% (74.3-84.7)	70.3% (61.3-77.6)
Median (IQR)	NR	17 years (8.18-NR)

IELSG-19: International Extranodal Lymphoma Study Group-19 study; IQR: interquartile range; LDH: serum lactate dehydrogenase; UNL: upper normal limit; IPI: International Prognostic Index; MALT-IPI: Mucosa-Associated Lymphoid Tissue lymphoma International Prognostic Index; PFS: progression-free survival, 95% CI: 95% confidence interval; OS: overall survival; NR: not reached. [a]Eastern Cooperative Oncology Group performance status reported in 282 cases in the validation set. [b]Reported in 264 cases in the validation set. [c]Assessed in only 289 patients in the test set and 168 in the validation set. [d]Defined in 281 patients in the validation set. [e]Defined in 267 patients in the validation set. [f]Other comprises: lenalidomide in combination with rituximab (15 patients), lenalidomide as a single agent (12 patients), interferon-α (4 patients), bortezomib (3 patients), thalidomide (2 patients), and ofatumomab (1 patient).

Methods

Patients

Details regarding the IELSG-19 randomized phase III trial (ClinicalTrials.gov Identifier: NCT 00210353) have been published elsewhere.[6,9] All patients provided written informed consent and the study was approved by the institutional review board or ethics committee of each institution involved. This trial compared chlorambucil alone to rituximab alone and to the combination of rituximab and chlorambucil as front-line therapy in EMZL patients, with event-free survival as the primary endpoint.[6]

Early POD was defined as in the follicular lymphoma study by Casulo *et al.*[8] Patients enrolled in the IELSG-19 study were divided into two groups: a group formed of patients with early POD, that is, progression within 24 months from the start of first-line treatment, and a reference group, consisting of patients without early POD. An independent validation set, comprising only patients who received front-line systemic treatment (chemotherapy, immunotherapy or both), was derived from the validation cohort of the MALT-IPI study, which included patients from different sources (the databases of the IELSG-1 multicenter study and of a retrospective survey conducted at the Oncology Institute of Southern Switzerland, and at the Hematology Division of the University of Eastern Piedmont, in Novara Italy, and a cohort of patients diagnosed at the Medical University of Vienna, Austria) whose details have also been published elsewhere.[7]

Statistical methods

Primary analysis of OS from risk-defining events was performed in both the test and validation sets, commencing the observation for the group with early POD from the time progression occurred, and for the reference group from 24 months after the start of front-line therapy.

Statistical analysis was performed using the Stata/SE 11.0 software package (StataCorpLP, College Station, TX, USA). The median follow-up was computed as the median time to censoring or death using the reverse Kaplan-Meier method.[10] Survival probabilities were calculated using life tables and survival curves were estimated by the method of Kaplan-Meier; differences between groups of patients were evaluated using the log-rank test.[11] Binomial exact 95% confidence intervals (95% CI) were calculat-

ed for proportions. The χ^2 test or Fisher exact test was used as appropriate for comparing proportions. Hazard ratios (HR) and their 95% confidence intervals (95% CI) were estimated using a Cox proportional hazard model. Multivariable analysis of clinical prognostic factors (including the international prognostic scores, IPI[12] and MALT-IPI[7]) for OS was performed by Cox regression[13] with backward stepwise selection. To identify factors associated with early POD, logistic regression was also performed with backwards stepwise selection. *P*-values <0.05 (two-sided test) were considered statistically significant.

Results

Test set

The analyzed population consisted of 401 patients enrolled in the IELSG-19 study, 131 treated with chlorambucil, 132 with chlorambucil and rituximab and 138 with rituximab; their main clinical features are summarized in Table 1. Estimated hazard curves showed that the peak risk of progression occurred within the first 24 months after diagnosis (Figure 1A). Among these 401 patients, 69 (17%) had early POD, relapsing within 24 months of starting treatment. Of the remaining 332 patients, 315 (79%) had no relapse or death during the first 24 months and form the reference group. Relapses were observed later in 64 (20%) patients in the reference group. Nine patients were lost to follow-up and eight patients died without POD within 24 months of starting treatment (Figure 2, left panel).

The median age of the 69 patients with early POD was 62 years (range: 31 to 81 years), 32 (46%) patients were male and 26 patients (38%) had a primary gastric localization (Table 2).

Early POD was most frequent in patients with Eastern Cooperative Oncology Group performance status >1 (*P*=0.042) and elevated serum LDH (*P*=0.002). Patients with early POD were more likely to have high-risk MALT-IPI scores (*P*=0.005) and high-risk IPI scores (*P*=0.013) than the reference group. In contrast, elevated serum β_2-microglobulin level, advanced disease stage (III-IV *vs*. I-II), multiple extranodal sites of involvement, primary site of disease localization (gastric *vs*. extra-gastric), age at diagnosis (with either 60 or 70 years cut-off) were not associated with early POD. An unbalanced distribution of patients with early POD was evident across the treatment arms, with early POD occurring more frequently (34/132, 26%) in the single agent rituximab arm and less frequently in the combination treatment arm (13/125, 10%) when compared with the standard arm of single agent chlorambucil (22/127, 17%) (χ^2 test, *P*=0.006) (Table 2).

In a stepwise logistic regression (including the above-mentioned individual factors predicting early POD at univariate analysis: treatment arm, LDH concentration, performance status, high-risk IPI score, high-risk MALT-IPI score), only high-risk MALT-IPI score retained statistical significance (*P*=0.006; odds ratio: 2.39; 95% CI: 1.29-4.45).

The proportion of subjects with early POD was also higher among patients achieving partial remission after first-line therapy than among complete responders (*P*<0.0001) and, notably, transformation into aggressive histology was detected more frequently in patients with early POD than in the reference group (7/69 *vs*. 3/315; *P*<0.0001).

With a median follow-up time of 7.4 years, 18 of 69 patients with early POD died and the OS rates at 5 and 10 years after the risk-defining event were 80% (95% CI: 69-88%) and 64% (95% CI: 45-78%), respectively, in the early POD group *versus* 91% (95% CI: 87-94%) and 85% (95% CI: 79-90%), respectively, in the reference group (HR=2.42; 95% CI: 1.35-4.35; log-rank *P*=0.002) (Figure 3A).

Early POD maintained its predictive power with regards to OS (after a risk-defining event) together with a high-risk MALT-IPI score and age (as a continuous variable) in a stepwise Cox model after controlling for treatment arm, LDH concentration, performance status, disease stage, age, B-symptoms, multiple extranodal sites and high-risk IPI groups (Table 3).

Table 2. The distribution of patients' characteristics in the test and validation sets according to whether they had early progression of disease or not.

	Test set (IELSG-19)			Validation set		
	Early POD subset	Reference subset	*P*-value	Early POD subset	Reference subset	*P*-value
Number of patients	69	315		64	160	
Median age at diagnosis (IQR)	62 years (40-78)	60 years (28-80)	0.667	64 years (31-87)	60 years (23-92)	0.410
Male/female ratio	32/37	153/162	0.741	24/40	67/93	0.547
Stage III-IV, n (%)	36 (52%)	131 (42%)	0.108	41 (64%)	68 (43%)	0.004
Performance status >1, n (%)	3 (4%)	2 (1%)	0.042	5 (8%)	6 (4%)	0.300
Lactate dehydrogenase >UNL, n (%)	14 (20%)	25 (8%)	0.002	18 (31%)	16 (11%)	<0.001
β_2 microglobulin >UNL, n (%)	36 (16%)	8 (16%)	0.906	15 (41%)	39 (41%)	0.957
Primary gastric lymphoma, n (%)	26 (38%)	136 (43%)	0.403	27 (42%)	71 (44%)	0.766
IPI, high-intermediate/high risk, n (%)	20 (29%)	51 (16%)	0.013	30 (48%)	40 (26%)	0.001
MALT-IPI, high risk, n (%)	19 (28%)	43 (14%)	0.005	25 (43%)	28 (19%)	0.001
First-line treatment, n (%)						
Chemotherapy	22 (32%)	105 (33%)		42 (66%)	85 (53%)	
Immuno-chemotherapy	13 (19%)	112 (36%)		11 (17%)	42 (26%)	
Immunotherapy	34 (49%)	98 (31%)	0.006	11 (17%)	33 (21%)	0.210
Median follow-up (IQR)	6.0 years (5.2-9.4)	8.0 years (5.9-9.9)	0.024	7.0 years (3.5-10.2)	6.9 years (4.3-10.9)	0.569

IELSG-19: International Extranodal Lymphoma Study Group-19 study; POD: progression of disease; IQR: interquartile range; LDH: serum lactate dehydrogenase; UNL: upper normal limit; IPI: International Prognostic Index; MALT-IPI, Mucosa-Associated Lymphoid Tissue lymphoma International Prognostic Index. *P*-values refer to the comparison of proportions in early POD *versus* reference subsets by a χ^2 or Fisher exact test, as appropriate.

Validation set

Table 1 shows the main characteristics of the patients in the validation cohort, which comprised 287 MALT lymphoma patients who received front-line systemic treatment (chemotherapy, immunotherapy or both). The median age of this set of patients was 63 years (range: 23 to 92 years). Most of these patients were female (60%).

Estimated hazard curves showed a peak risk of progression at approximately 24 months after diagnosis (Figure 1B). After a median follow-up of 5.7 years, 64 patients (22%) had early POD. Fifty-four patients had a follow-up shorter than 2 years and nine died without prior disease progression within 2 years of starting treatment (Figure 2, right panel). Hence, the reference cohort comprised 160 patients, among whom relapses were later observed in 51 (33%). The early POD rates were similar in the groups of patients receiving different initial therapy (chemotherapy alone, rituximab alone or rituximab combined with different chemotherapeutic or immunomodulatory agents). Similar to the testing cohort, the early POD group was enriched in cases with transformation to aggressive histology (6 of 64 *vs*. 3 of 160 patients in the reference group, P=0.018) and early POD was most frequent in patients with elevated LDH (P<0.001), high-risk MALT-IPI scores (P=0.001) and high-risk IPI scores (P=0.001) (Table 2). In addition, in the validation cohort, early POD was associated with advanced disease stage (P=0.004) (Table 2).

As in the IELSG-19 study cohort, the patients in the validation set who experienced early POD after systemic therapy had an increased risk of death (HR=2.15; 95% CI: 1.19-3.90; log-rank P=0.009). In the early-POD group, the 5-year OS rate was 70% (95% CI: 54-81%), and the 10-year OS rate was 48% (95% CI: 28-66%). In comparison, the 5-year OS rate in the reference group was 88% (95% CI: 80-93%), and the 10-year OS rate was 71% (95% CI: 58-81%) (Figure 3B).

Table 3. Multivariate analysis for overall survival in the test set (stepwise Cox model, 383 patients).

	HR	95% CI	*P*-value
Early POD	1.90	1.03-3.49	0.039
Age	1.13	1.08-1.18	<0.001
MALT-IPI high risk	2.71	1.43-5.13	0.002

HR: hazard ratio; 95% CI: 95% confidence interval; POD: progression of disease; MALT-IPI: Mucosa-Associated Lymphoid Tissue lymphoma International Prognostic Index.

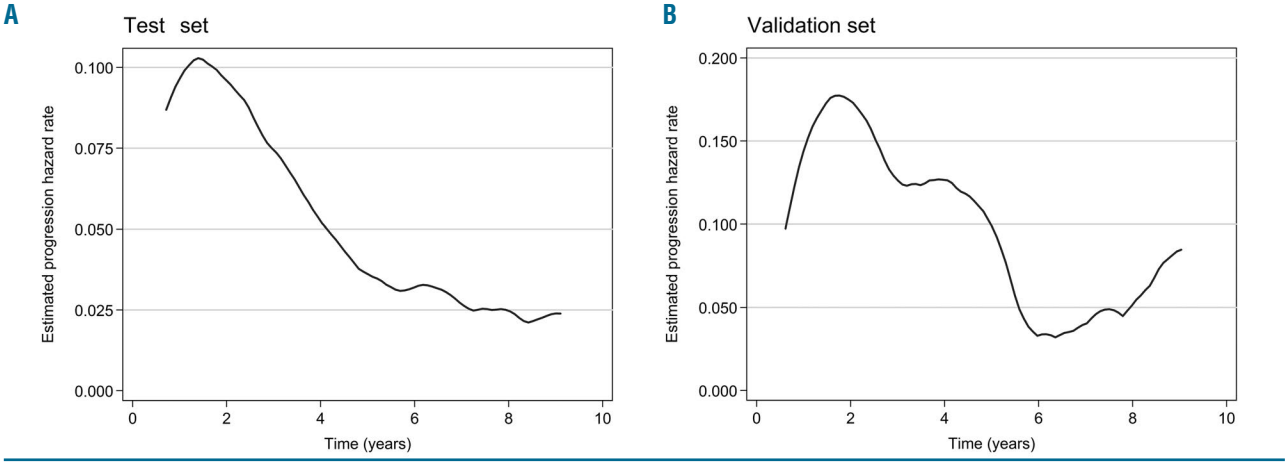

Figure 1. Risk of disease progression. (A, B) Estimated hazard of progression for patients in the test set, formed of a cohort of individuals from the International Extranodal Lymphoma Study Group-19 (IELSG-19) study (A) and for the patients included in the validation set (B).

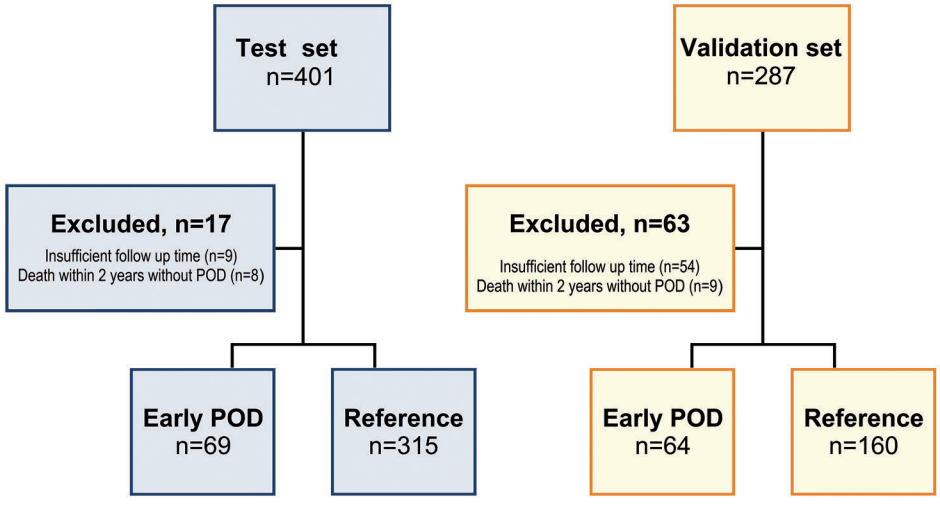

Figure 2. Patients' distribution. The selection and distribution of patients according to timing of disease progression in the test and validation sets. POD: progression of disease.

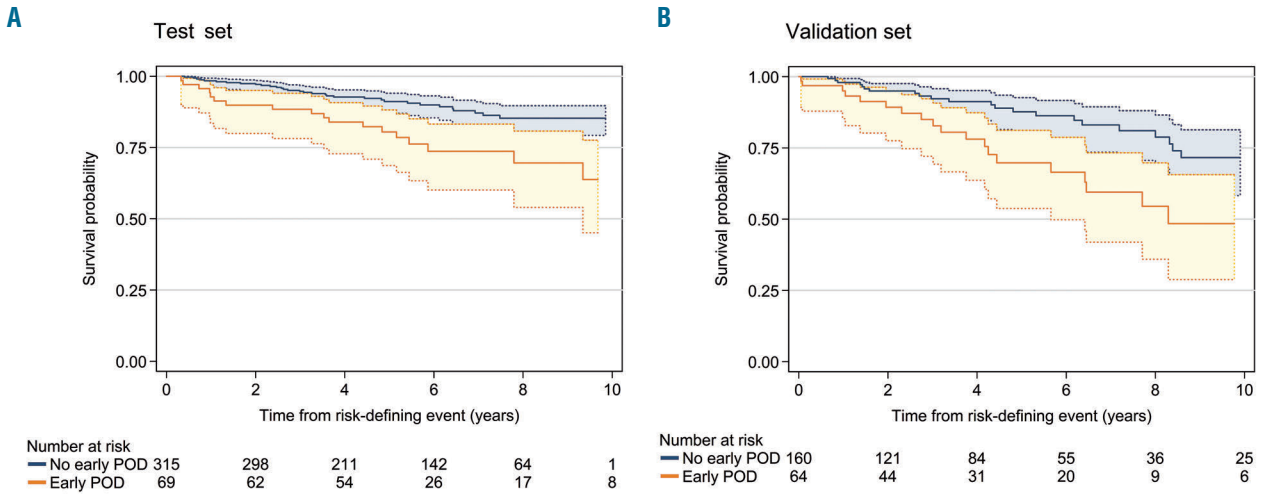

Figure 3. Overall survival. (A, B) Kaplan-Meier estimates of overall survival and their confidence intervals according to the occurrence of early progression of disease in patients enrolled in the International Extranodal Lymphoma Study Group-19 randomized clinical trial (A) and in the validation set of patients who received front-line systemic therapy (B). POD: progression of disease.

Discussion

The present study provides the first validated evidence that early POD, defined as lymphoma progression within 2 years after initial treatment, is a powerful tool to predict long-term survival in EMZL.

Early POD is a widely accepted survival predictor in follicular lymphoma,[8,14-18] with many studies showing that 20% of patients relapse within 2 years of treatment regardless of the addition of maintenance rituximab.[8] In a heterogeneous group of indolent non follicular B-cell lymphomas, a retrospective study from the Mayo Clinic and University of Iowa found that event-free survival at 12 months was associated with a better outcome.[19] However, in keeping with follicular lymphoma, the IELSG-19 study showed a PFS at 2 years of approximately 20%.[6] A large retrospective series from the University of Miami including only EMZL also showed similar PFS rates.[20] We therefore decided to maintain the 24-month time-span, already validated in follicular lymphoma, in our EMZL analysis. Our choice was further justified by the estimated hazard curves showing that the peak risk of progression occurred within 2 years.

A potential prognostic relevance of early POD was suggested by the abovementioned study from the University of Miami.[20] An observational study of non-follicular indolent lymphomas by the Italian Lymphoma Foundation (FIL) also found that early POD has a prognostic value in MZL.[21] However, none of these reports provided a thorough description of the clinical features of the EMZL patients with early POD and they did not include independent validation of their findings. Compared to these studies, the present study has additional strengths. It analyzed the impact of early POD in a cohort of patients prospectively collected in the largest controlled clinical trial performed so far in EMZL, with histological diagnosis confirmed by central pathology review and with uniformly defined follow-up investigations.

The external validation strengthens our findings. The prognostic impact of early POD in EMZL was confirmed in an independent cohort, obtained by merging three heterogeneous series of EMZL cases.[7] which included patients treated with a variety of conventional chemotherapy regimens and immunomodulatory agents in combination with rituximab or not. We showed that our results might be applied to both gastric and extra-gastric primary lymphomas, and to patients receiving different initial therapies.

Histological transformation of MZL is a well-recognized risk factor, which affects the clinical course of the disease.[22-24] The significant proportion of cases with evidence of transformation to aggressive histologies among patients relapsing early after systemic treatment may contribute to the inferior outcome seen in this study. This observation emphasizes the need for repeated histological evaluations, in particular in the case of early relapse, since cases with transformed histology require more intensive therapy.

In conclusion, we provide novel evidence that, in patients with EMZL who received front-line systemic treatment, early POD is associated with poor survival and should be further investigated as a potentially useful endpoint in future prospective clinical trials.

Acknowledgments

The authors thank the IELSG-19 study investigators, data managers, and nursing staff. The authors also thank Ayda Lüönd and Rita Gianascio Gianocca for excellent secretarial assistance.

Funding

This work was partly supported by the International Extranodal Lymphoma Study Group; by a grant from Oncosuisse (ICP OCS-01356-03-2003); AIRC 5 x 1000 (n. 21198), AIRC, Milan, Italy; and the AGING Project, Department of Excellence (DIMET), Universita' del Piemonte Orientale, Novara, Italy. The IELSG-19 clinical trial was supported in part by an unrestricted research grant from Roche International, Ltd. The funders had no role in study design, data collection, analysis, and interpretation, or writing of the report.

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