Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Mantle Cell Lymphoma of Mucosa-Associated Lymphoid Tissue

A European Mantle Cell Lymphoma Network Study

Morello, Lucia; Rattotti, Sara; Giordano, Laura; Jerkeman, Mats; van Meerten, Tom; Krawczyk, Katarzyna; Moita, Filipa; Marino, Dario; Ferrero, Simone; Szymczyk, Michał; Aurer, Igor; El-Galaly, Tarec Christoffer; Di Rocco, Alice; Visco, Carlo; Carli, Giuseppe; Defrancesco, Irene; Carlo-Stella, Carmelo; Dreyling, Martin; Santoro, Armando; Arcaini, Luca

Published in:
HemaSphere

DOI (link to publication from Publisher):
10.1097/HS9.0000000000000302

Creative Commons License
CC BY-NC-ND 4.0

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):
Morello, L., Rattotti, S., Giordano, L., Jerkeman, M., van Meerten, T., Krawczyk, K., Moita, F., Marino, D., Ferrero, S., Szymczyk, M., Aurer, I., El-Galaly, T. C., Di Rocco, A., Visco, C., Carli, G., Defrancesco, I., Carlo-Stella, C., Dreyling, M., Santoro, A., & Arcaini, L. (2020). Mantle Cell Lymphoma of Mucosa-Associated Lymphoid Tissue: A European Mantle Cell Lymphoma Network Study. *HemaSphere*, *4*(1), 1-6. Article e302. https://doi.org/10.1097/HS9.0000000000000302

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

HemaSphere
Powered by EHA

EUROPEAN HEMATOLOGY ASSOCIATION

Article
OPEN ACCESS

Mantle Cell Lymphoma of Mucosa-Associated Lymphoid Tissue: A European Mantle Cell Lymphoma Network Study

Lucia Morello[1], Sara Rattotti[2], Laura Giordano[3], Mats Jerkeman[4], Tom van Meerten[5], Katarzyna Krawczyk[6], Filipa Moita[7], Dario Marino[8], Simone Ferrero[9], Michał Szymczyk[10], Igor Aurer[11], Tarec Christoffer El-Galaly[12], Alice Di Rocco[13], Carlo Visco[14], Giuseppe Carli[15], Irene Defrancesco[2], Carmelo Carlo-Stella[1,16], Martin Dreyling[17], Armando Santoro[1,16], Luca Arcaini[2,18]

Correspondence: Luca Arcaini (e-mail: luca.arcaini@unipv.it).

Abstract

While classical nodal mantle cell lymphoma (cMCL) is often associated with involvement of multiple extranodal sites, isolated extranodal disease (ED) at the time of diagnosis is a rare event; data on the outcome of these forms are lacking. On behalf of the European MCL Network, we conducted a retrospective analysis on the clinical characteristics and outcomes of MCL presenting with isolated or predominant ED (MALT MCL). We collected data on 127 patients with MALT MCL diagnosed from 1998 to 2015: 78 patients (61%) were male with a median age of 65 years. The involved sites include: upper airways + Waldeyer ring (40; 32%), gastrointestinal tract (32; 25%), ocular adnexa (17; 13%), oral cavity and salivary glands (17; 13%) and others (13; 1%); 7 patients showed multiple extranodal sites. The median follow-up was 80 months (range: 6–182), 5-year progression-free survival (PFS) was 45% (95% CI: 35–54) and 5-year overall survival (OS) was 71% (95% CI: 62–79). In an explorative setting, we compared MALT MCL with a group of 128 cMCL patients: MALT MCL patients showed a significantly longer PFS and OS compared with nodal cMCL; with a median PFS of 4.5 years vs 2.8 years ($p = 0.001$) and median OS of 9.8 years vs 6.9 years ($p = 0.018$), respectively. Patients with MALT MCL at diagnosis showed a more favorable prognosis and indolent course than classical nodal type. This clinical variant of MCL should be acknowledged to avoid possible over-treatment.

Downloaded from https://journals.lww.com/hemasphere by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3R72+U4HWGwiOdEb6ZZPBJIG+8VXCdaAYXPMEtPCTDw= on 03/09/2020

Presented in abstract form at the 14th International Conference on Malignant Lymphoma, ICML-Lugano, Switzerland, June 2017 and at 45th annual meeting of the American Society of Hematology, Atlanta, GA, USA, December 2017.

Tarec Christoffer El-Galaly: Employment by Roche, Basel from 1st January 2019.

[1]Department of Oncology and Hematology, Humanitas Clinical and Research Center, Rozzano, Italy
[2]Division of Hematology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
[3]Biostatistic Unit, Humanitas Clinical and Research Center, Rozzano, Italy
[4]Department of Oncology, Skane University Hospital, SE-221 85 Lund, Sweden
[5]Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands
[6]Department of Hematology, Jagiellonian University, Kraków, Poland
[7]Instituto Português de Oncologia de Lisboa de Francisco Gentil, Lisbon, Portugal
[8]Oncology Unit 1 Veneto Institute of Oncology IOV-IRCCS, Padova, Italy
[9]Division of Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino, Italy
[10]Department of Lymphoid Malignancies, The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland
[11]Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, Croatia
[12]Department of Hematology, Aalborg University Hospital, Denmark
[13]Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy
[14]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy
[15]Department of Cell Therapy and Haematology, San Bortolo Hospital, Vicenza, Italy
[16]Department of Biomedical Sciences, Humanitas University, Rozzano, Italy
[17]Department of Medicine III, University Hospital LMU, Munich, Germany
[18]Department of Molecular Medicine, University of Pavia, Pavia, Italy

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

HemaSphere (2019) Vol:No

Received: 28 May 2019 / Received in final form: 10 September 2019 / Accepted: 17 September 2019

Citation: Morello L, Rattotti S, Giordano L, Jerkeman M, van Meerten T, Krawczyk K, Moita F, Marino D, Ferrero S, Szymczyk M, Aurer I, El-Galaly TC, Di Rocco A, Visco C, Carli G, Defrancesco I, Carlo-Stella C, Dreyling M, Santoro A, Arcaini L. Mantle Cell Lymphoma of Mucosa-Associated Lymphoid Tissue. *HemaSphere*, 2019;00:00. http://dx.doi.org/10.1097/HS9.0000000000000302

Introduction

In addition to classical nodal mantle cell lymphoma (cMCL), an aggressive disease requiring high-intensity chemotherapy,[1,2] the 2016 update of the WHO classification of lymphoid neoplasms recognizes the less common leukemic non-nodal variant (nnMCL), characterized by lymphocytosis and splenomegaly without nodal disease, showing an indolent clinical course.[3–5]

In particular, the leukemic nnMCL is represented by cells that have experienced follicular germinal center and carry IgVH somatic hypermutation with a discriminant gene-expression profiling;[7–8] this variant is frequently associated with a >7 years survival.[1] Correct identification of this variant has a potential clinical impact, since this subset of MCL can benefit from a watch-and-wait or a more conservative approach.[6]

Extranodal involvement in classical nodal MCL is common, and gastrointestinal tract is the most involved site, often found endoscopically in asymptomatic patients or as multiple lymphomatoid polyposis.[9,10] Infiltration of breast, lung, skin, soft tissue, salivary gland and orbit are also seen. Involvement of more than 2 extranodal sites occurs in 30% to 50% of patients. However, isolated extranodal disease (ED) is rarely detected in cMCL at diagnosis and only a few reports are available: therefore, in everyday clinical practice it is not possible to define the optimal treatment strategy.[11,12]

On behalf of the European MCL Network, we conducted a multicenter study, which collected MCL cases characterized by isolated or predominant extranodal disease (which we defined MALT MCL).

Patients and methods

Study design

This was a retrospective multicenter study conducted on behalf of the European MCL Network. Consecutive MCL subjects characterized by isolated or predominant ED were enrolled, from 1998 to 2015, by all participating centers. We captured baseline clinical, laboratory and pathology data, initial therapy, and active follow-up of all patients for relapse/progression and death in order to describe a possible variant of MCL with a peculiar clinical presentation in MALT sites.

Afterward, we compared MALT MCL with a group of classical nodal MCL patients consecutively diagnosed in the same period in 2 major Italian centers in order to describe, in an explorative intention, the outcomes and the distribution of prognostic factors between the 2 groups.

The study was approved by the Ethics Committee/institutional Review Boards/data protection agencies of participating sites. Patients provided written consent to participate when appropriate.

Selection criteria

All patients in the MALT MCL cohort were aged >18 years and presented at diagnosis with only extranodal site (ES) involvement or predominant extranodal disease with minimal locoregional lymphadenopathy defined as CT scan longest axis <2 cm. nnMCL characterized by splenomegaly and lymphocytosis without nodal involvement were excluded. Patients with involvement of tonsils and Waldeyer ring sites were also included in the extranodal group. Diagnosis of MCL was established according to the WHO classification criteria and confirmed by immunohistochemistry for cyclin D1 detection and/or FISH for translocation (11;14).

Staging procedures were not standardized but varied depending on different centers, they included chest and abdomen imaging investigations (computed tomography [CT]) and bone marrow biopsy in all patients; ultrasound [US] scans, digestive tract endoscopic investigations and ear, nose and throat (ENT) evaluation in selected cases.

In the comparative cohort, we included patients with classical nodal involvement with or without concomitant ED.

Statistical methods

Study endpoints included progression-free survival (PFS), early and late progression of disease (POD) and overall survival (OS), duration of response, time to next treatment and OS from relapse/progression (OS-2) [as defined in Supplementary material, Supplemental Digital Content, http://links.lww.com/HS/A46].

Data were summarized by descriptive statistics. Differences between groups were evaluated by the Chi-square test or t test (Fisher exact test and Wilcoxon test, when appropriate). Survival (OS and PFS) was estimated using the Kaplan-Meier method and differences between groups were evaluated by the log-rank test (or the trend test when appropriate).

Both in the univariable and multivariable analyses, the effect of clinical or demographical factors on survival were evaluated using the Cox proportional hazards model. In order to identify variables impacting OS and PFS in MCL, the following parameters were evaluated: gender, simplified prognostic index for advanced stage MCL (sMIPI),[13] Ki-67 index,[14] cytology,[15] Ann Arbor stage, bone marrow involvement, leukemic disease, splenomegaly, type of treatment (ASCT) and clinical variant of disease (MALT vs cMCL). ASCT was considered as a time-dependent variable.

A p-value <0.05 was considered statistically significant (2 sides). All statistics were performed using SAS version 9.4.

Results

Patients characteristics and treatment of MALT MCL

We collected data from 127 patients with MALT MCL in 14 European centers from 1998 to 2015.

Median age at diagnosis was 65 years (range: 36–85), patients were predominantly male (61%) with a good performance status (Eastern Cooperative Oncology Group 0 in 94 patients, 74%) and localized disease (Ann Arbor stage I/II in 73 patients, 57%) (Table 1). Twenty-seven patients showed a bone marrow involvement in addition to ES, and 2 patients had also leukemic disease. Histological and molecular features of MALT MCL patients are summarized in Table S1 (Supplemental Digital Content, http://links.lww.com/HS/A46).

Seventy-four patients (58%) with MALT MCL had minimal locoregional lymphadenopathy at diagnosis. Involved ES included: upper airways and Waldeyer ring (40 patients, 31%), gastrointestinal tract (32 patients, 25%), ocular adnexa (17 patients, 13%) oral cavity and salivary glands (17 patients, 13%). Other less frequent sites were skin (n=3), thyroid (n=3), breast (n=1), liver (n=1), testicle (n=1), bone (n=1), paranasal sinus (n=1), kidney (n=1), larynx (n=1) and in 7 patients multiple MALT sites were involved at diagnosis.

Table 1

Features of 127 patients with MALT mantle cell lymphoma and 128 patients with classical nodal mantle cell lymphoma

	MALT MCL		Nodal cMCL		
Feature	***N***	***%***	***N***	***%***	***p-value***
Sex					
Male	78	61	95	74	0.029
Female	49	39	33	26	
Age					
≤65 years	61	48	62	48	0.948
>65 years	66	52	66	52	
sMIPI					
Low	56	45	49	42	0.877
Intermediate	48	39	48	41	
High	20	16	20	17	
Missing	3		11		
Ann Arbor stage					
I/II	73	57	11	9	<0.001
III/IV	54	43	117	91	
Bone marrow involvement					
Negative	93	78	34	27	<0.001
Positive	27	22	90	73	
Missing	7		4		
Leukemic disease					
No	125	98	97	76	<0.001
Yes	2	2	31	24	
Ki-67 proliferation index					
Low (<30%)	45	63	52	53	0.219
High (≥30%)	27	37	46	47	
Missing	55			30	
Cytology					
Blastoid/pleomorhic	14	11	18	15	0.406
Classic	111	89	104	85	
Missing	2		6		
ECOG PS					
0	94	74	103	81	0.176
≥1	33	26	24	19	
Missing			1		
B symptoms					
No	84	68	105	83	0.006
Yes	39	32	21	17	
Missing	4		2		
ASCT					
No	97	76	75	59	0.002
Yes	30	24	53	41	
High-dose cytarabine					
No	83	67	72	57	0.111
Yes	41	33	54	43	
Missing	3		2		
Minimal adenopathy					
No	53	42			
Yes	74	58			

ASCT = autologous stem cell transplantation, ECOG = Eastern Cooperative Oncology Group, MALT = mucosa-associated lymphoid tissue, MCL = mantle cell lymphoma, MIPI = Mantle Cell Lymphoma International Prognostic Index, PS = performance status, cMCL = classical nodal MCL.

The majority of patients fell into the low and intermediate sMIPI categories (84%).

Most patients (94%) treated with chemotherapy regimen received concomitant rituximab; 41 patients received induction therapy containing high-dose cytarabine followed by ASCT in 30 cases (24%). Other induction therapies included R-CHOP-like (n=44) and R-bendamustine (n=6). Data on therapy were not available for three patients. A minority received rituximab single agent (n=4) or radiotherapy (n=27), and a watch-and-wait policy was chosen in only 2 patients.

Twenty-five patients (25/27; 92%) treated with radiotherapy alone had a limited stage of disease (stage 1). They experienced 5-year PFS and OS of 53% and 70%, respectively.

Patients who underwent ASCT were mainly in advanced stage (23/30; 77%) compared with those treated with more conservative regimens (31/97; 32%). Only 2 patients underwent allogenic stem cell transplantation after a relapse to ASCT.

Outcome and prognosis of MALT MCL

Overall response rate to the primary treatment was 97%, and median duration of response and time to next treatment were 31.1 months (range: 1.3–169.4) and 22.4 months (range: 0.6–85.5), respectively.

We observed 44 deaths (median follow-up 80 months; 6–182), of which 34% were due to disease progression. Other causes of death included: other neoplasms (8 patients, 28%), treatment-related toxicity (8 pts, 28%) and no known cause (13 patients, 45%).

Thirty-three patients relapsed, 82% of patients had isolated extranodal involvement and only four patients (12%) had systemic nodal disease. A total of 19% of patients (6/31) who received rituximab single-agent or RT alone relapsed.

During follow-up, 16 patients developed secondary malignancies (3 acute myeloid leukemia, 1 myelodysplastic syndrome and 12 solid neoplasia) corresponding to a cumulative incidence of 8.7% at 5 years. Median time from diagnosis to the second neoplasm was 17.6 months (6–106).

PFS and OS at 5 years was 45% (95% CI: 35–54) and 71% (95% CI: 62–79), respectively.

In the univariable analysis (Table 2), age >65 years, high sMIPI, ECOG ≥1 and bone marrow involvement showed a negative impact on PFS. In the multivariable model, only sMIPI confirmed its statistically significant effect. Factors affecting OS in univariable analysis (Table 2) were age >65 years, high sMIPI, ECOG ≥1 and Ki-67 ≥30%. In the multivariable analysis, sMIPI and Ki-67 confirmed their statistically significant impact on OS. The effect of transplant on PFS (hazard ratio [HR]: 0.59, 95% CI: 0.29–1.19; p=0.139) and OS (HR: 0.58, 95% CI: 0.24–1.38; p=0.215) was not significant even when adjusted for the other factors.

In MALT MCL, we did not observe a different outcome according to cytology (5-year PFS of 46% vs 44% for blastoid and classic cytology, respectively) and type of ES.

Early POD occurred in 18/43 (42%) patients. OS-2 for patients with early and late POD was 35.4% and 69.1% at 5 years, respectively (p=0.002). Patients with late POD had an extremely favorable prognosis (median OS-2 not reached).

Comparison with nodal MCL

MALT MCL patients were compared to 128 patients with cMCL (Table 1). Median age was 65 years in both cohorts. We observed a slightly higher female prevalence in the MALT MCL cohort (39% vs 26%; p=0.029). The unfavorable features as high sMIPI, Ki-67 ≥30% and blastoid/pleomorphic cytology showed a homogenous distribution in the 2 groups. Patients with MALT MCL had lower LDH values (p=0.002) at diagnosis and a more often limited disease (stage I/II) than patients with cMCL (57% vs 9%, respectively; p<0.001).

Regarding secondary ES in cMCL, 57 patients (44%) presented with at least one extranodal involvement at diagnosis

Table 2

Univariable analysis for progression-free survival and overall survival in 127 patients with MALT mantle cell lymphoma

	PFS		OS	
Factor	***5-year (%)***	***p-value***	***5-year (%)***	***p-value***
All	44.8		71.1	
Sex				
Male	42.8	0.808	69.3	0.76
Female	47.3		73.4	
Age				
≤65 years	59.3	<0.001	89.1	<0.001
>65 years	31		54.3	
sMIPI				
Low	55.7	<0.001[a]	91.7	<0.001[a]
Intermediate	43.3		57.6	
High	15.6		37	
Ann Arbor stage				
I/II	52.7	0.098	72.5	0.656
III/IV	31.3		69.3	
Bone marrow involvement				
Negative	50.8	0.037	75.8	0.091
Positive	15.7		57.3	
ECOG PS				
0	56.4	<0.001	81.1	<0.001
≥1	13.1		43.5	
Ki-67 proliferation index				
Low (<30%)	41.7	0.052	80	0.002
High (≥30%)	38.1		54.7	
Cytology				
Blastoid/pleomorphic	46.4	0.993	54.2	0.332
Classic	44		72.7	
B symptoms				
No	44.4	0.438	75.5	0.161
Yes	43.8		62	
ASCT	0.59 (0.29–1.19)[b]	0.139	0.58 (0.24–1.38)[b]	0.215
Minimal locoregional adenopathy				
No	43.2	0.595	64.2	0.478
Yes	46.1		76.2	

ASCT = autologous stem cell transplantation, ECOG = Eastern Cooperative Oncology Group, MALT = mucosa-associated lymphoid tissue, MCL = mantle cell lymphoma, MIPI = Mantle Cell Lymphoma International Prognostic Index, PFS = progression-free survival; PS = performance status.

[a] trend test.

[b] HR (95% CI).

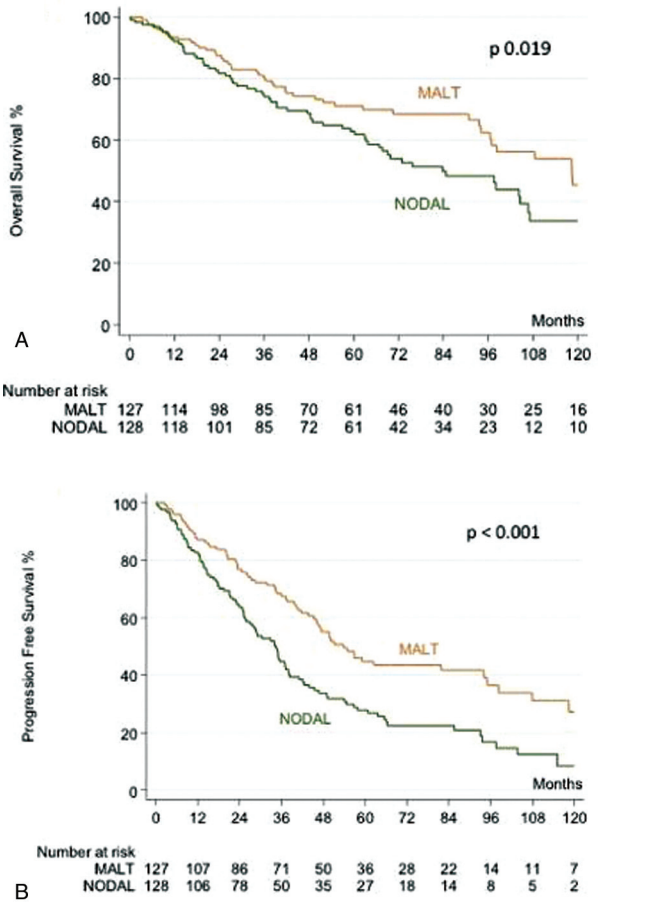

Figure 1. Comparison of the overall survival of 127 patients with MALT mantle cell lymphoma and of 128 patients with classical nodal mantle cell lymphoma (A) and comparison of the progression-free survival of 127 patients with MALT mantle cell lymphoma and of 128 patients with nodal classic mantle cell lymphoma (B).

in addition to bone marrow (gastrointestinal tract in 21 patients, Waldeyer's ring in 12 patients and multiple ES in 14 patients).

Regarding treatment, cMCL were treated with more intensive regimens compared with the MALT type; 41% and 24% of patients underwent ASCT (p = 0.002), respectively. No patient in the nodal cMCL group was treated with radiotherapy alone.

Median follow-up was 85.4 months (range: 6–218) and was not different from that of MALT MCL. The incidence of secondary malignancies was similar between the 2 groups.

MALT MCL patients showed a longer OS and PFS compared with cMCL: median OS 9.8 years vs 6.9 years (5-year OS: 71% vs 63%; HR: 0.63, 95% CI: 0.43–0.92; p = 0.017) and median PFS 4.5 years vs 2.8 years, respectively (5-year PFS: 45% vs 28%; HR: 0.54, 95% CI: 0.40–0.75; p < 0.001) (Fig. 1). In addition, when comparing only MALT patients with Waldeyer ring involvement to cMCL we observed that PFS was longer for MALT MCL than nodal type (p = 0.01).

Univariable analysis for PFS and OS of the cMCL cohort is summarized in Table S2 (Supplemental Digital Content, http://links.lww.com/HS/A46).

When restricting the analysis to patients with unfavorable cytology (blastoid/pleomorphic variant), PFS was significantly longer in MALT MCL compared with cMCL (Fig. S1, Supplemental Digital Content, http://links.lww.com/HS/A46).

To evaluate the prognostic impact of proposed novel clinical variant of the disease, a model was constructed in the whole population considering the clinical variant as a variable (MALT vs cMCL). In the whole MCL population, in the univariable analysis, factors affected PFS were age >65 years, stage III/IV, bone marrow involvement, ECOG ≥1, Ki-67 ≥30%, blastoid/pleomorphic cytology and no ASCT. In the univariable model for OS, all investigating factors for PFS remained significant except stage III/IV (Table S3, Supplemental Digital Content, http://links.lww.com/HS/A46). Clinical disease variant resulted as an independent prognostic factor for PFS (HR: 0.57; 95% CI: 0.37–0.86; p = 0.007) adjusted for all factors which confirmed their effect (Table 3).

The introduction of Ki-67 proliferation index into the multivariable model reduced the number of observations (from 241 to 165) and events (from 151 to 105 for PFS and from 99 to 67 for OS) due to the large number of missing data. Since Ki-67 constitutes a known strong prognostic factor that cannot be excluded from the analysis, we built the model comprising it (Table 3).

Table 3

Multivariable analysis for progression-free survival and overall survival in the whole mantle cell lymphoma population (127 patients with MALT mantle cell lymphoma and in 128 patients with nodal classic mantle cell lymphoma)

	PFS			OS		
Parameter	***HR***	***95% CI***	***p-value***	***HR***	***95% CI***	***p-value***
MALT MCL vs nodal cMCL	0.57	0.37–0.86	0.007	0.76	0.46–1.27	0.302
sMIPI (low vs high)	0.54	0.31–0.94	0.030	0.19	0.09–0.39	<0.001
sMIPI (intermediate vs high)	0.86	0.50–1.46	0.570	0.41	0.22–0.75	0.004
ASCT (yes vs no)	0.46	0.29–0.72	0.001	0.28	0.14–0.57	<0.001
Ki-67 proliferation index (high vs low)	1.96	1.30–2.97	0.001	2.28	1.36–3.83	0.002

ASCT = autologous stem cell transplantation, HR = hazard ratio, MALT = mucosa-associated lymphoid tissue, MCL = mantle cell lymphoma, MIPI = Mantle Cell Lymphoma International Prognostic Index.

In the multivariable model for OS without Ki-67 index, MALT presentation was a factor with a prognostic impact (HR: 0.65; 95% CI: 0.43–0.98; p=0.042) adjusted for MIPI and transplant status.

Discussion

Two major clinical and biological variants of MCL are described: in addition to the most common classical nodal MCL, a non-nodal variant characterized by splenomegaly and leukemic involvement with an indolent clinical course is widely described.[16]

In this retrospective series, we described a peculiar presentation of MCL characterized by ED in the absence or with minimal nodal involvement, which we can define as *MALT-oma like MCL* due to its similarity to MALT lymphomas.

The starting hypothesis underlying the project comes from the everyday clinical observation that patients with extranodal MCL seemed to present a more indolent behavior compared with nodal type. Therefore, we settled with a study within the European Mantle Cell network centers to confirm this clinical observation. The main objective of the study is purely descriptive of this clinical variant; the hypothesis of a difference in terms of outcome between the 2 groups (extranodal and nodal) has an exploratory intention only.

The frequent involvement of gastrointestinal tract in classic nodal MCL is well-known. In one study, 26% of patients with MCL presented with gastrointestinal symptoms at diagnosis; however, MCL infiltration was present histologically in the lower gastrointestinal tract in 88% and in the upper gastrointestinal tract in 43% of patients.[9] In our series of MALT MCL, 12 patients presented with upper gastrointestinal tract involvement while 13 had involvement of the lower tract and seven patients showed a simultaneous involvement of upper and lower gastrointestinal tract.

In our comparative cMCL series, the main secondary ES were GI and Waldeyer ring while typical MALT sites, such as salivary glands, ocular adnexa, and skin, were more frequently involved in MALT MCL than in classical nodal cases.

We decided to include isolated Waldeyer ring cases, although Waldeyer ring was listed as a nodal site in recent recommendations.[17] However, in most studies the Waldeyer ring is historically considered as an ES.[18] Interestingly, in our cohort, there was no difference in outcome within MALT MCL cohort according to the type of ES; on the other hand, the difference was still significant between the cMCL and MCL of the Waldeyer ring.

The majority of MALT MCL cases presented with minimal locoregional lymphadenopathy, but as for MALT marginal zone lymphomas,[19] the primary site of lymphoma involvement was defined as the clinically dominant ES, which requires diagnostic approach and to which primary treatment must often be directed. On the other hand, no patients showed distant adenopathy and during the course of disease, 82% of relapses were in ES while only four patients relapsed with systemic nodal disease. Noteworthy, the presence of locoregional lymphoadenopathy did not affect the prognosis.

We also want to underline that patients in the MALT MCL group with advanced stage (54 patients) or leukemic phase (2 patients) were included in the analysis because they showed a predominantly extranodal disease in addition to bone marrow involvement or leukemic disease. Majority of cases were stage IV for multiple extranodal sites or diffuse extranodal involvement.

In addition, the clinical features at presentation seem to be different in MALT MCL: female prevalence is higher in respect to cMCL, LDH is less frequently elevated and limited disease at initial staging is more common.

Patients with MALT MCL showed prolonged PFS and OS compared with the classic nodal variant. In addition, the extranodal variant of MCL was found to be an independent prognostic factor for PFS, defining a better outcome. In a multivariable model for OS, MALT MCL variant was associated with a reduction of the risk but failed to reach significance; in the model without Ki-67 index, MALT localization was a factor with a prognostic impact adjusted for MIPI and transplant status.

Regarding the impact of transplant on outcome, in MALT MCL we did not observe a statistically significant effect of transplantation, differing from nodal MCL. However, this should not be interpreted as a different impact of ASCT in the 2 groups since as the effect of ASCT is protective in both; the absence of significance is probably due a smaller sample size, and a larger series would be needed to settle this issue. Nevertheless, MALT patients, although undergoing ASCT less frequently, still had a better prognosis and could not benefit from a more intensive therapy.

Strengths of our study include the systematic collection and analysis of a large series of patients with a rare MCL clinical variant treated in the rituximab era, the homogeneous distribution of the baseline characteristics at diagnosis (cytology, Ki-67 and MIPI), the consecutive collection during the same time period as the controls and the comparable follow-up. Limitations include the possible lack of some clinical prognostic data, not standardized staging procedures between the centers and the absence of a centralized pathological review to identify biological markers able to recognize this clinical entity. In particular, the impact on outcome of cytology could not be better investigated due to the low prevalence of blastoid cytology in MALT and nodal MCL (14 and 18 patients, respectively). In addition, we do not have data in this setting on activity of new drugs, such as ibrutinib[20] and lenalidomide.[21]

In conclusion, this study identified a novel clinical variant of MCL, predominantly extranodal, with a more favorable prognosis and a more indolent course than the classical nodal type. The possible diagnosis of this peculiar presentation of MCL in MALT sites should be recognized, a possible overtreatment with intensive approaches may be omitted and an initial watch and wait strategy could be chosen in asymptomatic patients. Additional research is needed in this form of MCL in order to attribute its cellular origin and evaluate any molecular analogies with classic MCL, nnMCL and with marginal zone lymphomas.

Acknowledgements

The authors thank the investigators participating in the study and belonging to European Mantle Cell Lymphoma Network for their help in handling the data.
Editorial assistance was provided by Luca Giacomelli, PhD, and Aashni Shah (Polistudium), this assistance was supported by internal funds.

References

1. Maddocks K. Update on mantle cell lymphoma. *Blood.* 2018;132: 1647–1656.
2. Herrmann A, Hoster E, Zwingers T, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. *J Clin Oncol.* 2009;27:511–518.
3. Lynch RC, Gratzinger D, Advani R. Clinical impact of the 2016 update to the WHO lymphoma classification. *Curr Treat Options Oncol.* 2017; 18:45.
4. Orchard J, Garand R, Davis Z, et al. A subset of t(11;14) lymphoma with mantle cell features displays mutated IgVH genes and includes patients with good prognosis, nonnodal disease. *Blood.* 2003;101: 4975–4981.
5. Navarro A, Clot G, Royo C, et al. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biological and clinical features. *Cancer Res.* 2012;72:5307–5316.
6. Abrisqueta P, Scott DW, Slack GW, et al. Observation as the initial management strategy in patients with mantle cell lymphoma. *Ann Oncol.* 2017;28:2489–2495.
7. Nordström L, Sernbo S, Eden P, et al. SOX11 and TP53 add prognostic information to MIPI in a homogenously treated cohort of mantle cell lymphoma–a Nordic Lymphoma Group study. *Br J Haematol.* 2014;166:98–108.
8. Clot G, Jares P, Ginè E, et al. A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome. *Blood.* 2018;132:413–422.
9. Romaguera JE, Medeiros LJ, Hagemeister FB, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. *Cancer.* 2003;97:586–591.
10. Salar A, Juanpere N, Bellosillo B, et al. Gastro-intestinal involvement in mantle cell lymphoma: a prospective clinic, endoscopic, and pathologic study. *Am J Surg Pathol.* 2006;30:1274–1280.
11. Siddiqui UM, Rao SN, Galera PK, et al. Mantle cell lymphoma in the thyroid: a rare presentation. *Case Rep Pathol.* 2017;2017:6749801.
12. Yang P, Lin J, Liu H, et al. Primary bone mantle cell lymphoma with multiple vertebral compression fractures: a case report. *Oncol Lett.* 2017;13:1288–1292.
13. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood.* 2008;111: 558–565.
14. Hoster E, Rosenwald A, Berger F, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the European Mantle Cell Lymphoma Network. *J Clin Oncol.* 2016;34:1386–1394.
15. Bernard M, Gressin R, Lefrère F, et al. Blastic variant of mantle cell lymphoma: A rare but highly aggressive subtype. *Leukemia.* 2001; 15:1785–1791.
16. Ondrejka SL, Lai R, Smith SD, et al. Indolent mantle cell leukemia: a clinicopathological variant characterized by isolated lymphocytosis, interstitial bone marrow involvement, kappa light chain restriction, and good prognosis. *Haematologica.* 2011;96:1121–1127.
17. Cheson BD, Fisher RI, Barrington SF, et al. Reccommendations for initial evaluation, staging, and response assessment of Hodgkin and non Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32:3059–3068.
18. Oh SY, Kim WS, Kim JS, et al. Waldeyer's ring marginal zone B cell lymphoma: are the clinical and prognostic features nodal or extranodal? A study by the Consortium for Improving Survival of Lymphoma (CISL). *Int J Hematol.* 2012;96:631–637.
19. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood.* 2003; 101:2489–2495.
20. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *Br J Haematol.* 2017;179:430–4389.
21. Trněný M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. *Lancet Oncol.* 2016;17:319–331.