Management of the Marginal Zone Lymphomas

Barbara Vannata, Anastasios Stathis and Emanuele Zucca

Abstract

Marginal zone lymphomas (MZL) represent around 8 % of all non-Hodgkin lymphomas. During the last decades a number of studies have addressed the mechanisms underlying the disease development. Extranodal MZL lymphoma usually arises in mucosal sites where lymphocytes are not normally present from a background of either autoimmune processes, such as Hashimoto thyroiditis or Sjögren syndrome or chronic infectious conditions. In the context of a persistent antigenic stimulation, successive genetic abnormalities can progressively hit a B-cell clone among the reactive B-cells of the chronic inflammatory tissue and give rise to a MALT lymphoma. The best evidence of an etiopathogenetic link is available for the association between Helicobacter pylori-positive gastritis and gastric MALT lymphoma. Indeed, a successful eradication of this micro-organism with antibiotics can be followed by gastric MALT lymphoma regression in more than 2/3 of cases. Other microbial agents have been implicated in the pathogenesis of MZL arising in the skin (Borrelia burgdorferi), in the ocular adnexa (Chlamydophila psittaci), and in the small intestine (Campylobacter jejuni). The prevalence of hepatitis C virus (HCV) has also been reported higher in MZL patients (particularly of the splenic type) than in the control population, suggesting a possible causative role of the virus. In non-gastric MALT lymphoma and in splenic MZL the role of the antimicrobial therapy is, however, less clear.This review summarizes the recent advances in Marginal Zone Lymphomas, addressing the critical points in their diagnosis, staging and clinical management.

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Contents

1 Definition and Classification

Marginal zone lymphomas (MZL) represent a group of lymphomas that originate from B lymphocytes normally present in the "marginal zone," which is the external part of the secondary lymphoid follicles. MZLs develop in spleen, mucosa-associated lymphoid tissue (MALT), and/or in lymph nodes. In the most recent WHO classification, the MZL category comprises three different subtypes with specific diagnostic criteria, different behavior, and therapeutic implications: the extranodal MZL of mucosa-associated lymphoid tissue type (MALT lymphoma), the splenic MZL with or without villous lymphocytes (SMZL), and nodal MZL (NMZL) [1].

2 Epidemiology and Pathogenesis

Primary splenic and nodal MZLs are rare, each accounting for approximately less than 2 % of the non-Hodgkin lymphomas (NHLs). The extranodal MZLs of MALT type represent around 7–8 % of the NHL, including both the common gastrointestinal and the less usual non-gastrointestinal localizations [1].

MALT lymphoma B cells present somatically mutated IGHV genes in all cases with a pattern of somatic hypermutation and intraclonal variations suggesting that the tumor cells have undergone antigen selection and that their expansion may remain antigen-driven [2, 3]. Indeed, MALT lymphoma usually arises in mucosal sites where lymphocytes are not normally present and where MALT is acquired in response to either autoimmune processes, such as Hashimoto thyroiditis, Sjögren syndrome, or chronic infectious conditions. It is believed that, in the context of a persistent antigenic stimulation, additional genetic abnormalities may progressively affect a B-cell clone among the reactive B cells of the chronic inflammatory tissue and give rise to a MALT lymphoma.

The stomach is the most common site of localization, and the remission of most gastric MALT lymphomas after eradication of *Helicobacter pylori* (HP) strongly indicates a pathogenetic link between tumor cell proliferation and chronic *H. pylori*-induced inflammation [2]. Moreover, other infectious agents may have a putative role in non-gastric MZL pathogenesis at different sites: *Borrelia burgdorferi* in cutaneous lymphomas [4], *Chlamydophila psittaci* in the lymphoma of the ocular adnexa [5–7], and *Campylobacter jejuni* in small intestine lymphoma [8]. The prevalence of hepatitis C virus (HCV) infection has also been reported higher in patients with MZLs (particularly of splenic and nodal type) than in the control population [9, 10], suggesting a possible causative role of the viral agent [11]. In extranodal MZL, HCV seems more often present in non-gastric lymphomas, particularly in patients with subcutaneous [12] or salivary gland [13] involvement.

At least four recurrent chromosomal aberrations—the apparently mutually exclusive translocations t(11; 18)(q21; q21), t(1;14)(p22; q32), t(14; 18)(q32; q21), and the 6q23.3 deletion—have been reported in MALT lymphomas to affect the same signaling pathway, resulting in the activation of nuclear factor kappa B (NF-κB), a transcription factor with a central role in immunity, inflammation, and apoptosis [14–20]. The occurrence of the translocations varies according to the anatomical site, and their incidence and distribution may also have geographical differences, possibly reflecting different genetic backgrounds of either the patients or the infectious agents [21].

These site-specific biological differences might influence outcome and therapeutic approaches. Indeed, while antibiotic therapy is nowadays well established as the standard of care in patients with *H. pylori*-associated gastric MALT lymphoma, much less is known about the value of anti-infectious therapy in non-gastric MALT lymphomas and in non-MALT cases, where the standard treatment is less well defined.

3 Diagnosis

The diagnosis of MZL should be made in accordance with the current WHO classification [1].

It is advisable that the diagnosis is confirmed by an expert hematopathologist since differentiation from other lymphomas that can mimic MZLs is not always straightforward. A minimum immunohistochemistry panel is therefore recommended and it should include CD20, CD10, CD5, and cyclin D1 [22]. The presence of lymphoepithelial lesions, despite being very typical of MALT lymphoma, is not essential for the diagnosis as they can be seen both in some reactive conditions and in other indolent lymphomas. For extranodal MZL, assessment of a potential-associated histologic transformation is essential and, since the term "high-grade MALT lymphomas" is no longer accepted in the current WHO classification, the cases with solid or sheet-like proliferation of transformed large cells have to be diagnosed as diffuse large B-cell lymphomas [23].

At present, the diagnosis of SMZL does not strictly require a splenectomy [24]. In fact, following the analysis of cases in which the diagnosis has been confirmed by review of splenic histology, characteristic features to allow a diagnosis based on bone marrow examination and peripheral blood flow cytometry have been established, [25, 26]. Cytoplasmic villi may not be present in all cases and not all cases with villous lymphocytes will necessarily correspond to a SMZL; sometimes a definitive diagnosis may not be possible without splenectomy (which may not be required as treatment) [24].

4 Clinical Characteristics

4.1 Extranodal MZL (MALT Lymphoma)

MALT lymphoma is a neoplasm of adults with a median age at presentation of 60 years and a slight predominance in females. This type of lymphoma usually remains localized for a prolonged period within the tissue of origin, but involvement of regional lymph nodes and dissemination to multiple sites may occur. The stomach is the most common location, but MALT lymphoma has been described in several non-gastric sites, such as salivary gland, thyroid, skin, conjunctiva, larynx, lung, breast, kidney, liver, prostate, and also intracranial dura. Within the stomach, the disease is usually multifocal and concomitant gastrointestinal (GI) or non-GI involvement can be detected in 20 % of the cases. Disseminated disease is more common in non-GI MALT lymphomas, in which it is reported in up to one-quarter of the cases [27–30]. Bone marrow infiltration is described in up to 20 % of the cases [2, 31], while constitutional B-symptoms are rarely seen at diagnosis. Patients with lymph node or bone marrow involvement at presentation, but not those with involvement of multiple mucosal sites, are associated with a worse prognosis [27].

4.2 Splenic MZL

Splenic MZL (SMZL) is a disseminated disease at diagnosis in around 95 % of the cases. SMZL comprise around 20 % of MZLs, and it has usually an indolent course with overall survival ranging from 5 to 10 years. In around one-third of the cases, median survival is less than 4 years [32]. Histological transformation to DLBCL is rare (10–20 % of the patients) and is associated with a worse outcome. SMZL mainly affects elderly or middle-aged patients, with a median age of 65 years. SMZL is characterized by massive splenomegaly with minimal or absent lymphadenopathy, other than in the splenic hilum, and no other extranodal involvement, except bone marrow and liver. Cytopenias and lymphocytosis are frequently observed. When circulating villous lymphocytes are prominent, the term "splenic lymphoma with villous lymphocyte" has often been used in the past. Several reports have shown an epidemiological association between hepatitis C chronic infection and splenic and nodal MZLs. The strength of the relation between HCV and lymphomas has been found to be highly variable among countries, although HCV seems involved in the lymphomagenesis at least in a portion of cases. The best evidence of a causal link between HCV and lymphomas came from the observation of SMZL regression after antiviral therapy, first reported in 2002 by Hermine et al. [9], who described nine patients with splenic marginal zone lymphoma who had a lymphoma remission following interferon-α and ribavirin treatment. In the same report, six patients with SMZL, but without HCV infection, had no hematologic response to the antiviral therapy, thus ruling out a direct antitumor effect of interferon-α. These results were reproduced by other groups [33], showing that antiviral treatment with interferon-α with or without ribavirin can be an effective treatment for the majority of HCV-associated marginal zone lymphomas.

Around one-third of patients present a small serum monoclonal protein, mainly of IgM subtype. Sometimes, in HCV cases, the presence of cryoglobulins is detected. Autoimmune phenomena are seen in 15 % of the cases and comprise autoimmune hemolytic anemia, immune thrombocytopenia, cold agglutinin, antiphospholipid antibodies, acquired von Willebrand disease, and angioedema due to acquired C1-esterase inhibitor deficiency [32].

An Italian lymphoma cooperative group (Intergruppo Italiano Linfomi, IIL) developed a score model in 309 patients based on three risk factors (Hb less than 12 g/dl; albumin less than 3.5 g/dl; and LDH greater than normal). Patients were divided into three risk group with a 5-year OS of 88, 73, and 50 % for low-intermediate- and high-risk group, respectively [34]. Recently, a newer prognostic model (named HPLL on the basis of determinant factors, hemoglobin concentration, platelet count, high lactate dehydrogenase level, and extrahilar lymphadenopathy) has been developed by the SMZL Study Group from an international retrospective survey of 593 patients [35]. The HPLL score allowed to identify three risk groups with significantly different 5-year lymphoma-specific survival (94, 78 and 69 %, respectively) and appeared to have a better discriminative power than the

IIL score. Despite the fact that their clinical utility has not yet been confirmed in prospective studies, these indices are expected to improve the selection of patients for risk-tailored treatment approaches.

4.3 Nodal MZL

This lymphoma is rather uncommon, it comprises 10 % of MZLs and occurs in adults with a median age of 60 years, but it has also been reported in children. NMZL shares morphologic and immunophenotypic similarities with the other MZLs, and its differential diagnosis from other indolent lymphoma, in particular from lymphoplasmacytic lymphoma, is often very difficult [36–40]. Mutations of the MYD88 gene have been recently reported to occur in the large majority of lymphoplasmacytic lymphomas, and it is not usually present in MZL, thus making this finding very useful for the differential diagnosis [41].

NMZL presents with disseminated lymphadenopathy (mostly cervical and abdominal), with or without bone marrow and blood involvement at diagnosis in the vast majority of the cases [38]. The disease is often advanced at diagnosis, but usually patients do not have B-symptoms [42, 43]. A primary extranodal marginal zone lymphoma has to be ruled out, since around one-third of the cases represent nodal dissemination of a MALT lymphoma. In 10 % of the patients, a small monoclonal component, mainly of IgM-type, is detected [38].

OS of patients with NMZL is around 60 % at 5 years in most studies [38]. In a retrospective series of 93 patients analyzed by the International Lymphoma Study Group for the Non-Hodgkin's Lymphoma Classification Project, the OS for NMZL has been reported to be lower than that of patients with MALT lymphoma (56 % vs. 81 %, at 5 years, respectively) [44].

5 Staging

Extensive staging assessment is indicated in all MZL types, regardless of their presentation site [24]. It should include a history and physical examination; complete blood cell counts and basic biochemical studies, including evaluation of renal and liver function; LDH and β2-microglobulin levels; serum protein immunofixation; human immunodeficiency virus (HIV); hepatitis B (HBV) and C virus (HCV) serologies; CT scan of the chest, abdomen, and pelvis; and bone marrow aspirate and biopsy. Site-specific recommended procedures for MALT lymphoma staging are reported in Table 1. Gastroduodenal endoscopy (EGD) with multiple biopsies is also recommended to exclude gastric involvement in all cases of disseminated MZL. Localized MALT lymphoma is often multifocal within the involved organ (i.e., stomach and skin); nevertheless, this may not reflect a truly disseminated disease.

Table 1 Site-specific work-up procedures for extranodal MZL of MALT type

Site	Procedure
Gastric MALT lymphoma	
Stomach	• Endoscopic ultrasound
	• *H. pylori* status (by IHC)[a]
	• FISH or molecular assay for the t(11;18) translocation
Non-gastric MALT lymphoma	
Breast	• Mammography and MRI (or CT scan)
Intestine, small	• Endoscopy
	• Small bowel series (double contrast X-ray examination of the small intestine)
	• *Campylobacter Jejuni* search in the tumor biopsy by PCR, IHC or in situ hybridization
Intestine, large	• Colonoscopy
Lung	• Bronchoscopy + Broncho-alveolar lavage
Ocular adnexa	• MRI (or CT scan)
	• Ophthalmologic examination
	• *Chlamydophila psittaci* in the tumor biopsy and PBMNCs by PCR
Salivary glands	• ENT examination and echography
Skin	• *Borrelia Burgdorferi* in the tumor biopsy by PCR
Thyroid	• Echography ± CT scan of the neck thyroid function tests

IHC immune histochemistry, *MRI* magnetic resonance imaging, *CT* compute tomography, *PBMNCs* peripheral blood mononuclear cells, *PCR* polymerase chain reaction, *ENT* ear nose throat

[a]Breath test and serology studies for HP detection are recommended when the results of histology are negative

The value of the positron emission tomography (PET) scan is still unclear. In general, the use of PET-CT scan in the routine staging of MZL is not recommended [22, 24], except for selected cases (i.e., when a transformation to high-grade lymphoma is suspected). However, there is some evidence that many non-gastric sites are usually PET-positive [31]. In a meta-analysis of the published literature, the pooled detection rate of 18F-FDG PET or PET/CT in MALT lymphoma was 71 % and appeared particularly high in the pulmonary (94 %) and head and neck (90 %) localizations, showing that this type of lymphoma can often be FDG-avid and suggesting a potential clinical role of PET/CT in the initial evaluation of these patients, especially when the disease is apparently localized and radiotherapy is planned [45].

6 Treatment

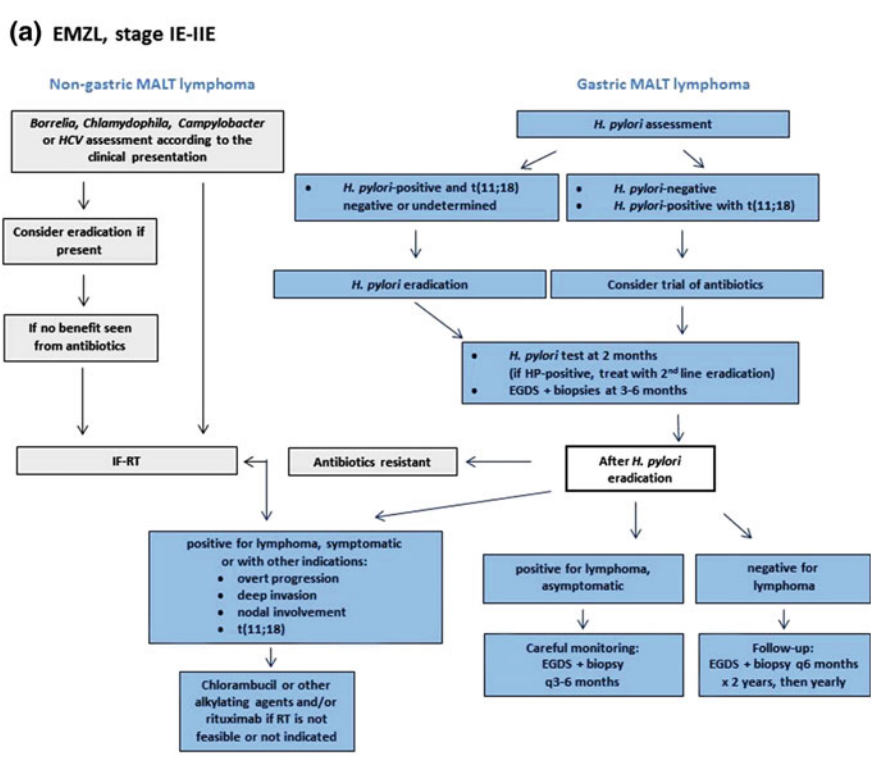
6.1 Extranodal MZL of MALT Type

The aforementioned etiologic association with some chronic infections has therapeutic implications in patients with MZL. Indeed, *H. pylori* eradication with antibiotics can lead to gastric MALT lymphoma regression in 60–100 % of the cases [46–51]. Anti-infectious treatments for non-gastric MZL are, however, largely investigational.

6.2 Gastric Marginal Zone Lymphoma of MALT Type, HP Positive

Figure 1 reports the algorithm of our treatment recommendation for limited and advanced-stage HP-positive gastric MALT lymphoma. Eradication of *H. pylori* with antibiotics should be the sole initial therapy for localized *H. pylori*-positive gastric MALT lymphoma, where this treatment can induce lymphoma regression and long-term clinical disease control in most patients [2]. Several effective anti-HP treatments are available. The choice should be based on the epidemiology of the infection and on the expected antibiotic resistance in different countries. The most commonly used regimen comprises a proton pump inhibitor (PPI) associated with clarithromycin and amoxicillin, administered for 10–14 days. Metronidazole can be used instead of amoxicillin for penicillin-allergic patients. Other regimens comprising H2-blockers or bismuth can be also effective. Breath test for *H. pylori* assessment should be repeated at least six weeks after the eradication therapy and at least two weeks after withdrawal of the PPI. In case of HP-eradication failure, a second-line therapy should be tried with a different triple- or a quadruple-therapy regimen [22] (Table 2). Histological remission is usually achieved within six months from *H. pylori* eradication. However, the length of time necessary to obtain a lymphoma regression ranges from very few months to more than 12 months. Hence, it is reasonable to wait for at least 12 months before starting another treatment in patients who achieve a clinical and endoscopic remission together with eradication of *H. pylori*, although histological residual lymphoma persists [2, 52]. The interpretation of the residual lymphoid infiltrate post-treatment in gastric biopsies can be very difficult. Differences in the response criteria adopted in the individual studies may explain the wide range of reported remission rates. Indeed, there are no uniform criteria for the definition of histological remission [2, 52]. Comparison with previous biopsies should be carried out to assess response, and we recommend the Group d'Etude des Lymphomes de l'Adult (GELA) scoring system as a reproducible method [53] (Table 3).

In fact, histological evaluation of gastric biopsies repeated on a fixed schedule is crucial for the follow-up in order to rule out either the disease persistence or the appearance of early epithelial changes, which may indicate an incoming gastric


(a) EMZL, stage IE-IIE
Non-gastric MALT lymphoma
Gastric MALT lymphoma
Borrelia, Chlamydophila, Campylobacter or HCV assessment according to the clinical presentation
H. pylori assessment
Consider eradication if present
H. pylori-positive and t(11;18) negative or undetermined
H. pylori-negative
H. pylori-positive with t(11;18)
If no benefit seen from antibiotics
H. pylori eradication
Consider trial of antibiotics
H. pylori test at 2 months (if HP-positive, treat with 2nd line eradication)
EGDS + biopsies at 3-6 months
IF-RT
Antibiotics resistant
After H. pylori eradication
positive for lymphoma, symptomatic or with other indications:
overt progression
deep invasion
nodal involvement
t(11;18)
positive for lymphoma, asymptomatic
negative for lymphoma
Careful monitoring: EGDS + biopsy q3-6 months
Follow-up: EGDS + biopsy q6 months x 2 years, then yearly
Chlorambucil or other alkylating agents and/or rituximab if RT is not feasible or not indicated
(b) EMZL, stage III-IV
Non-gastric MALT lymphoma
Gastric MALT lymphoma
Borrelia, Chlamydophila, Campylobacter or HCV assessment according to the clinical presentation
H. pylori assessment
consider eradication if the infection is present
eradication if H. pylori is present
Asymptomatic
Symptomatic
or with other indications to treat:
overt progression
bulky disease
organ damage
patient wish
Asymptomatic
Wait and see
Wait and see EGDS and biopsies every 3-6 months
Chemotherapy and/or rituximab, or consider including in clinical trials

◀ **Fig. 1** Algorithm for the treatment of patients with localized (Panel **a**) or disseminated (Panel **b**) MALT lymphomas. In principle, to remove an antigenic stimulation that may favor a relapse, eradication of putative driver chronic infections (*H. pylori* for gastric lymphomas, *B. burgdorferi* for cutaneous lymphoma, *C. psittaci* for lymphoma of the ocular adnexa, *C. jejuni* for IPSID, and *HCV* for salivary glands or subcutaneous lymphomas) should be given also to patients with disseminated disease together with the required lymphoma treatment. This may reduce the risk of gastric cancer in patients with *H. pylori* gastritis and liver cancer in those with chronic *HCV* infection

Table 2 Schedules for *H. pylori* eradication

Scheme	Drugs	Recommendation
Triple therapy	• PPI (standard dose mg twice daily)	• First line (low prevalence of clarithromycin resistance)
	• Clarithromycin (500 mg twice daily)[a]	
	• Amoxicillin (1,000 mg twice daily) for 10–14 days	
Triple therapy	• PPI (standard dose mg twice daily)	• First line (low prevalence of clarithromycin resistance)
	• Clarithromycin (500 mg twice daily)[a]	
	• metronidazole (400 or 500 mg twice daily)[b] for 10–14 days	
Quadruple therapy	• PPI (standard dose mg twice daily)	• First line (high prevalence of clarithromycin resistance)
	• Metronidazole (500 mg three times a day)	
	• Tetracycline 500 mg four times a day	
	• Bismuth sub citrate 120 mg four times a day for 10–14 days	• Second-line treatment[c]

[a]Triple therapy is recommended in areas where the prevalence of clarithromycin resistance is less than 10–15 %

[b]The use of metronidazole instead of amoxicillin is suggested in area with less than 40 % metronidazole resistance or in penicillin-allergic patients

[c]PPI plus amoxicillin, tetracycline, and metronidazole are recommended when bismuth is not available. When a third choice in needed, it should be based on the antimicrobial susceptibility test

carcinoma development, especially when *H. pylori* infection persists. Once *H. pylori* eradication has been demonstrated (by breath test or by a monoclonal stool antigen test), it is recommended to repeat EGD with multiple biopsies 2–3 months after treatment to exclude lymphoma progression, and subsequently (every 6 months for 2 years) to monitor the histological lymphoma regression [22].

Gastric MALT lymphoma less commonly spreads to distant organs, and the frequency of the histological transformation into diffuse large B-cell lymphoma (DLBCL) is low. Transient histological relapses can be observed in endoscopic biopsies during long-term follow-up, but they tend to be self-limiting, and especially without the stimulus from *H. pylori* reinfection, they do not implicate a true clinical relapse. Hence, when persistent but not progressive residual disease or histological relapse is documented, a "wait and see" policy seems safe [46, 49, 54, 55]. Nevertheless, a long-term careful endoscopic and systemic follow-up (clinical examination, blood counts and minimal adequate radiological or ultrasound examinations

Table 3 GELA criteria for post-treatment histological evaluation of gastric endoscopic biopsies in gastric—MALT lymphoma [53]

Gela grading score	
CR, complete histological remission	• Normal or empty LP and/or
	• Fibrosis with absent or scattered plasma cells and small lymphoid cells in the LP
	• No LEL
pMRD, probable minimal residual disease	• Normal or empty LP and/or
	• Fibrosis with aggregates of lymphoid cells or lymphoid nodules in the LP/MM
	• Focal or absent LEL
rRD, responding residual disease	• Focal empty LP and/or
	• Fibrosis with dense, diffuse, or nodular lymphoid infiltrate extending around glands in the LP
	• Focal or absent LEL
NC, no change	• Dense, diffuse, or nodular lymphoid infiltrate
	• LEL usually present

LP lamina propria, *LEL* lymphoepithelial lesions, *MM* muscolaris mucosa, *SM* submucosa

every 12–18 months) is strongly advisable for all patients. Furthermore, the risk of gastric adenocarcinoma among individuals with gastric MALT lymphoma has been reported to be six fold higher, while the risk of other non-Hodgkin lymphomas should be considered higher than in the general population [56, 57].

An obvious prerequisite for a response to antibiotics is the presence of a *H. pylori* infection. However, there are reports of lymphoma regression following antibiotics also in *H. pylori*-negative patients, and first-line therapy with antibiotics has to be considered at least in those patients without the t(11;18) translocation, possibly due to a false-negative test or to infection by other Helicobacter species [52]. The response rates of lymphomas are around 70-90 % for the mucosa-confined lymphomas and decrease for the tumors infiltrating the submucosa, the muscularis propria, and the serosa [58–62]. At the same time, the involvement of perigastric lymph nodes, detected by either CT scan or endoscopic ultrasound, rarely respond to antibiotics [60–62]. Moreover, the presence of a high-grade lymphoma component and a history of autoimmune disease were associated with antibiotic therapy resistance [63]. Nearly all gastric lymphomas with t(11;18) translocation will not respond to *H. pylori* eradication therapy [62, 64]. The t(11;18) is also associated with the resistance to chlorambucil or thalidomide as single agents [65, 66]. Notably, data on a very small series of 13 patients have suggested that the combination of chlorambucil and rituximab is active in t(11;18)-positive cases [67].

H. pylori eradication therapy should be considered in all gastric MALT lymphomas, independent of the stage [22], but patients with symptomatic disseminated disease should also be considered for systemic treatment, e.g., the combination of rituximab and chemotherapy. The role of immunochemotherapy will be further discussed in the following sections which present the management of non-gastric presentations.

6.3 Gastric HP-Negative or Antibiotic-Resistant MALT Lymphoma and Non-gastric MALT Lymphoma

No definite guidelines exist for the management of patients with *H. pylori*-negative gastric-lymphoma, for patients failing anti-HP treatment, or for the non-gastric localizations. In *H. pylori*-negative cases, a regression of the lymphoma after antibiotic treatment is unlikely and the immediate start of oncological treatments should be considered. Nevertheless, a course of anti-HP treatment may be considered since occasional lymphoma responses have been reported [2, 52]. An oncological treatment should, eventually, be considered when no signs of lymphoma regression are seen at a repeated endoscopy assessment 2–3 months after antibiotics administration. No significant survival difference between patients who received different initial treatments (including chemotherapy alone, surgery alone, surgery with additional chemotherapy, and radiation therapy) has been shown [68, 69]. Radiotherapy may be the favored choice for patients with localized disease HP-negative or for patients who do not achieve a lymphoma regression following antibiotic therapy [70]. Indeed, involved-field radiotherapy to the stomach and perigastric lymph nodes has results in excellent disease control and most reports support the use of a moderate dose (24–30 Gy given in 3–4 weeks) [71–74].

Radiotherapy has become a standard treatment, at least in North America, also for most non-gastric localized presentations. Literature reports a high rate of local control in MALT lymphoma, with a high proportion of patients likely to be cured [75–84]. The use of radiotherapy in this setting has been recommended by the NCCN Clinical Practice Guidelines in Oncology [85]. The modern radiotherapy techniques, such as three-dimensional conformal radiotherapy and intensity modulated radiotherapy, allow an accurate determination of the clinical target volume, thus reducing the toxicity to surrounding organs [73, 86]. The curative doses required (25–35 Gy) are generally associated with mild and reversible acute toxicity and a low risk of long-term side effects, although special caution should be given for specific localizations such as the ocular adnexa or the lung [72, 73, 74, 86].

In patients with disseminated non-gastric MALT lymphoma, observation with a careful monitoring can be often an adequate initial approach. When treatment is required, there is no consensus for the choice of treatment, but rituximab alone or chemotherapy with or without rituximab appear the most appropriate choice. The treatment approach of disseminated MALT lymphomas is the same in patients with primary gastric and non-gastric origin, and the enrollment in controlled clinical trials is advisable. Indeed, there is no standard recommendation, as only a limited number of drugs and regimens have been specifically tested in MALT lymphomas [2]. Oral alkylating agents (either cyclophosphamide or chlorambucil) or purine nucleoside analogues (fludarabine, cladribine) are active as single agents [87, 88]. Rituximab monotherapy has also been tested in phase II studies [89, 90]. However, there is not yet a widely accepted standard immunochemotherapy regimen. Recently, the efficacy and safety of the combination of rituximab plus chlorambucil has been proven in a phase III study of the International Extranodal Lymphoma

Study Group (IELSG) in gastric (failing antibiotics) or non-gastric MALT lymphomas. In comparison with either rituximab or chlorambucil given as single agent, chlorambucil plus rituximab resulted in significantly superior complete remission, progression-free and event-free survival rates; however, no overall survival benefit was shown [91, 92]. The combination of rituximab and bendamustine [93] as well as the combination of fludarabine and rituximab has also shown high rates of disease control in smaller non-randomized studies [93]. However, the hematological and infectious toxicity observed with the latter regimen, both during and after therapy, was significant in this patient population [94]. Aggressive anthracycline-containing chemotherapy regimen should be reserved for patients with high tumor burden (bulky masses, unfavorable International Prognostic Index) or for those with histological transformation [95].

6.4 Antibiotic Treatment in Non-gastric MALT Lymphoma

The role of antibiotic therapy in patients with non-gastric MALT lymphoma is unclear [96]. Some anecdotal reports described regressions of non-gastric MALT lymphomas in *H. pylori*-infected patients after *H. pylori* eradication [97–99], but this approach is not effective in the majority of patients with non-gastric localization [100]. Antibiotic therapy appears nowadays a reasonable first-line therapy for patients with ocular adnexa MALT lymphoma and may be considered for some cutaneous marginal zone lymphoma; however, it remains experimental in other non-GI localization of MALT lymphomas.

6.5 Antibiotic Therapy for Ocular Adnexa MALT Lymphoma (OAMZL)

The finding that *Chlamydophila psittaci* has been detected in up to 80 % of Italian patients with OAMZL provided the rationale for the antibiotic treatment of localized lesions [5, 7], and a pivotal Italian experience showed that the eradication of *C. psittaci* infection using doxycycline for patients with OAMZL may result in lymphoma regression in approximately 50 % of patients, including pre-treated patients and patients with regional lymph node involvement [101, 102]. Following this first demonstration, a prospective international phase II study was later conducted by the IELSG. In this study, *C. psittaci* DNA was detected in nearly 90 % of the lymphoma biopsy specimens. Thirty-four patients were treated front line with doxycycline and assessed for chlamydia eradication and lymphoma response. Chlamydia eradication was achieved in 14/34 patients (48 %), and six patients obtained a complete lymphoma regression (overall response rate, ORR 65 %). At a median follow-up of 37 months, the 5-year progression-free survival was 55 %. Moreover, in this study, a consistent concordance between *C. psittaci* detected in tumor tissue and *C. psittaci* on conjunctival swab indicated that conjunctival swab may be a

simple, noninvasive tool for monitoring the infection [6]. Globally, doxycycline has been tested in 120 patients with OAMZL, with an ORR of around 50 % [96]. The median time for response after antibiotic therapy is 6 months. Analogous to *H. pylori* eradication in gastric MALT lymphoma [52], in some patients, responses are slow and may require up to 36 months [102]. Further investigations are warranted to clarify the appropriate time for starting a different treatment after doxycycline failure, the optimal schedule of doxycycline as well as to identify other potential infective agents, and improve the eradicative antibiotic efficacy [6, 103, 104].

6.6 Antibiotic Therapy for Primary Cutaneous Marginal Zone Lymphoma (PCMZL)

The term "pseudolymphoma" refers to a typical cutaneous B-cell infiltration known to be induced by *Borrelia burgdorferi* chronic infection. *B. burgdorferi* has also been reported to have a potential pathogenetic role in marginal zone lymphomas of the skin. Some case reports have shown that the eradication of *B. burgdorferi* following ceftriaxone therapy resulted in regression of an associated cutaneous marginal zone lymphoma [4]. However, the evidence is based on a limited number of patients [96], and therefore, no recommendations can be made.

6.7 Immunoproliferative Small Intestinal Disease (IPSID)

IPSID has a long natural history, often over many years, including a potentially reversible early phase. If left untreated, however, the lymphoma can undergo a histologic transformation to a DLBCL. In its early phases, IPSID can be treated with prolonged antibiotic therapy (i.e., tetracycline or metronidazole and ampicillin for at least 6 months), which can lead to lymphoma regression. These results may suggest a role for an infectious agent, *Campylobacter jejuni* seeming the best candidate [8]. Anthracycline-containing regimens, combined with nutritional support plus antibiotics to control diarrhea and malabsorption, represent the best chance of cure for patients with advanced-stage disease. Surgery has no therapeutic role, since the lymphoma usually diffusely involves the intestine.

6.8 Splenic MZL

Most patients with SMZL can initially be managed with a "wait and see" strategy. Cytopenia or symptomatic massive splenomegaly is the main indication for treatment start. When treatment is needed, therapeutic options are splenectomy, chemotherapy, and rituximab alone or in combination with chemotherapy [24].

Splenectomy has been for a long time the therapy of choice. It allows prolonged remissions with rapid alleviation of splenomegaly-related symptoms, accompanied

by resolution of cytopenia and disappearance of circulating lymphocytes in around 90 % of the cases. Even when bone marrow involvement and lymphocytosis persist, the time to next treatment may be longer than 5 years [32]. However, SMZL is a systemic disease, and splenectomy cannot be considered a curative option. Moreover, it is a major surgical procedure with significant morbidity and non-negligible mortality, especially in older patients [105].

There is no evidence for a survival benefit when chemotherapy is added to splenectomy. Chemotherapy alone has been used for patients unsuitable for splenectomy or relapsing after surgery. Alkylating agents (i.e., chlorambucil or cyclophosphamide) alone or in combination (i.e., CHOP) with fludarabine monotherapy have shown to be effective. More recently, since most patients are elderly and at high risk for surgery, frontline immunotherapy with rituximab alone or in combination with chemotherapy has become more and more widely used [105–109]. In a Greek study, 58 patients were treated with rituximab at a dose of 375 mg/m^2 per week for 6 weeks as induction, followed by rituximab maintenance in 43 patients (375 mg/m^2 every 2 months for 1–2 years). The overall response rate in this study was 95 %, with almost half of responses being complete, while the 5-year progression-free survival was 77 %. Maintenance therapy with rituximab appeared to induce a significantly longer response duration (the 5-year progression-free survival was 84 % for patients receiving maintenance and 36 % for patients without maintenance) [108].

A survey on the survival outcomes after surgery or rituximab-based systemic therapy in the Surveillance Epidemiology and End Results-Medicare database (SEER) included 227 patients, diagnosed between 2000 and 2007, and treated with splenectomy (68 %), rituximab alone (23 %) or in combination with chemotherapy (9 %) within 2 years from diagnosis. It showed higher rates of hospitalizations, infections, transfusions, and cardiovascular or thromboembolic events after chemoimmunotherapy than after splenectomy. Conversely, there was no significant difference in the complication rates between groups treated with splenectomy or rituximab alone [109].

Other retrospective series of rituximab monotherapy, including both chemotherapy-naive and refractory patients, showed overall responses of 88–100 % with marked and prompt regression of splenomegaly and improvement of cytopenias with overall survival comparable to that reported after splenectomy. Sustained responses occurred both with and without rituximab maintenance and relapsed patients responded to second courses of rituximab monotherapy [106]. The remission rates and durations after rituximab, given either alone or with chemotherapy, were significantly better than after chemotherapy without rituximab in the same patients, with manageable toxicity [107]. The combination of rituximab with chemotherapy may further improve progression-free survival, but further evaluation with confirmatory prospective trials is warranted [105–107]. The available evidence, despite being mainly based on retrospective studies, seems to suggest that rituximab could replace splenectomy as first-line treatment, particularly in SMZL patients over the age of 65 years. In these patients, the risk of lymphoma-related death and overall survival were similar to rituximab or splenectomy as initial

therapy, indicating that single-agent rituximab may carry the most favorable risk/benefit ratio in this population [109], but optimal schedule and long-term outcome have not been fully defined yet.

For patients with SMZL HCV-associated, there is evidence that antiviral treatment may be an acceptable option. As already mentioned, the use of antiviral therapy to treat HCV-associated lymphomas was established after the demonstration by Hermine et al. [9] of splenic marginal zone lymphoma regression following HCV eradication. Later, other reports confirmed that antiviral therapy can be an efficacious frontline therapy for HCV-associated SMZL and nodal MZL [10, 12, 110, 111]. HCV-RNA clearance is needed to attain lymphoma response [111], and the achievement of a virologic response can be followed by a lymphoma regression in up to 75 % of the cases. At present, in HCV-positive patients with marginal zone lymphoma who do not need immediate conventional treatment for lymphoma, antiviral treatment with pegylated-interferon-α and ribavirin should be considered as first-line treatment [24, 111]. However, novel and better tolerated antiviral agents are under development and will hopefully make easier the treatment of both lymphoma and hepatitis. Indeed, less toxic and shorter interferon-free regimens will very soon become a suitable option, and this may be particularly advantageous for the treatment of lymphoma patients with interferon-resistant HCV genotypes [112, 113].

6.9 Nodal MZL

At present, no large prospective trials have been published and there are no definite guidelines for the management of NMZL. It is generally accepted that treatment should be planned according to the therapeutic principles adopted for follicular lymphomas [24]. Therefore, patients affected by NMZL are often treated with a combination of immunotherapy with anti-CD20 monoclonal antibody alone or in combination with chemotherapy. Good responses are in general reported across studies. However, relapses are frequent [114, 115]. In young patients with early relapse, high-dose chemotherapy with autologous stem cell transplantation may be an option, while radiotherapy, using low doses of radiation, may be considered in localized cases or as palliative treatment of symptomatic lesions [36, 38]. However, none of these approaches has been prospectively tested.

Analogous to SMZL, in patients with HCV-associated chronic infection, elimination of the infection may induce a subsequent lymphoma regression [111]; therefore, an attempt to achieve HCV eradication with interferon and ribavirin should be considered before any other treatment in patients who do not require immediate immunochemotherapy. The role of new antiviral agents remains to be evaluated.

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