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Marginal Zone Lymphoma Perge Progredi, Next on the Horizon

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Abstract

Marginal Zone Lymphoma (MZL) is a clonal indolent mature B-cell malignancy. MZL accounts for 10% of all Non-Hodgkin Lymphomas (NHL). The common etiologic hallmarks of MZL are chronic antigenic B-cell stimulation, which leads to increased DNA replication errors and genomic instability. Standard therapy for MZL has been watch and wait, cytotoxic chemotherapy, surgery, and/or radiation therapy based on clinical risk factors. However, novel developments of targeted therapies have brought new excitement to MZL therapeutic armamentarium. In this article, we provide an update on the novel diagnostic approaches to MZL as well as innovative molecular targets that will ultimately become the next therapeutic paradigm for patients with MZL.

Keywords: Marginal zone lymphoma; Helicobacter pylori; MALT lymphoma

Introduction

Marginal zone lymphoma

Marginal zone lymphoma (MZL) is a clonal indolent mature B-cell malignancy, and accounts for 10% of all non-Hodgkin lymphomas (NHLs). According to the 2008 World Health Organization classification (WHO), MZL comprises three distinct clinical entities: extranodal MZL of the mucosa-associated lymphatic tissue (MALT), splenic MZL (SMZL), and nodal MZL (NMZL) [1]. Morphologically, MZL is similar to other indolent B-cell lymphomas such as follicular lymphoma (FL), hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and mantle cell lymphoma (MCL), therefore diagnosis can be challenging. Morphology is still the most important criteria for diagnosis, but morphology alone maybe insufficient, as the additional immunophenotypic analysis is routinely required and molecular genetic data are now vital to proper diagnosis. Some entities are associated with infectious complications such as *Helicobacter pylori (H. pylori)* or autoimmune/rheumatologic disorders. Molecular subtypes of MZL often have characteristic recurrent chromosomal abnormalities by fluorescent in situ hybridization (FISH), which have been identified [2]. Ideally, for each lymphoma, a "stem cell of origin" is postulated and identification of the clone is critical to the diagnosis. Therefore, sufficient tissue biopsy for morphologic/immunophenotypic/molecular analysis in consultation with an expert hematopathologist is imperative to properly diagnosing MZL.

MALT lymphoma

MALT lymphoma is the most common subtype of MZL [3]. Majority of patients present with localized disease. Bone marrow involvement is uncommon, and approximately, 25% present with extensive disease at diagnosis [4]. Clinical symptoms of MALT lymphoma are insidious and include weight loss, abdominal pain, nausea, and vomiting [5]. Diagnosis of gastric MALT lymphoma requires an endoscopic examination, which may reveal erythema, ulceration, or a solitary mass. Immunohistochemical or flow cytometric analysis of tissue sections includes screening for B- and T-cell markers in addition to kappa and lambda light chain expression and CCND1 (Cyclin D1), BCL2, and BCL6. MALT lymphoma is characterized by cluster of differentiation (CD) 5 negative, CD10 negative, CD20 positive, CD23 +/-, CD42+/- and CCND1, BCL2 and BCL6 negative.

(Tables 1 and 2, illustrating common clinical and laboratory finding for each subtype of MZL)

The most common site of disease involvement is the stomach, which is classically associated with chronic infectious stimulation by *H. pylori*. It was originally described by Parsonnet et al. [6]. The clinical association between *H. pylori* infection and gastric lymphoma but it was not until early 2000s that the Japanese's group finally came up with the molecular link between the two entities. In murine models, *H. pylori* were shown to produce CagA protein, which secreted into gastric epithelial cell and induces aberrant activation of SHP-2 tyrosine phosphatase a known oncoprotein controlling differentiation and proliferation [7,8]. Therapeutic implications of eradicating *H. pylori* have been well documented and its treatment results in regression of MALT lymphoma, regardless of disease stage or histologic grade [9].

Common cytogenetic aberration reported in gastric MALT lymphoma is the t(11;18), which has also been seen in *H. pylori*-negative cases [10]. Recurrent cytogenetic markers such as t(11;18), which generates the fusion transcript between *API2* and *MALT1*, are seen in approximately 10%-30% of MALT lymphomas and at higher frequencies in gastric (30%) and lung MALT lymphomas (40%). Translocation (14;18) between IgH and MALT1 is seen in approximately 10% of MALT lymphomas of the liver, lung, and ocular adnexae. One other translocation involving *FOXP1* and *IGH*, t(3;14), leads to the overexpression of FOXP1 and is seen in fewer than 10% of MALT lymphomas and is commonly associated with MALT lymphomas of the thyroid, ocular adnexae, and skin. In fewer than 5% of MALT lymphomas, t(1;14), between *BCL10* and IgH, leads to overexpression of BCL10. MicroRNA expression profiling has enhanced the distinction between MALT lymphomas and diffuse large B-cell lymphomas [1]. MYC continues to represent a key player by which MALT lymphomas evolve to diffuse large B-cell lymphomas [11]. Myc appears to modulate key microRNAs in the nuclear factor-kappa B (NF-κB) signaling pathway and that DNA hypermethylation of key tumor suppressor

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	Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma	Nodal Marginal Zone Lymphoma (NMZL)	Splenic Marginal Zone Lymphoma (SMZL)
Clinical Characteristics	• Mostly present as localized disease • Stomach is the most common site of involvement. • Other typical site include other GI sites, salivary, ocular adnexa, thyroid, lungs, skin and breast • Symptoms will depend on the location of the lesion	• Diffuse peripheral nodal involvement	• Splenomegaly and cytopenias • Bone marrow is commonly involved • Early satiety • Abdominal bloating
Morphology			
Immunophenotype			
Positive	CD 19, 20, 22, 79a, IgG, BCL-2		
Negative	CD 5, 10, 23, 103, Cyclin D1 and BCL6		
Associated Infections	Helicobacter Pylori, C Jejuni, C. psittaci and B. burgdorferi	Unknown	Hepatitis C virus
Cytogenetic Abnormalities	t(11;18) BIRC-MALT1 t(14;18) IGHV-MALT1 t(1;14) IGHV-BCL10 t(3;14) IGHV-FOXP1 del 6q TNFAIP3	No typical cytogenic aberration	+3q +12q

Table 1: Subtypes of MZL.

Organ	Associated Condition
Stomach	Helicobacter pylori
Small bowel	Campylobacter Jejuni
Thyroid	Hashimoto Thyroiditis
Parotid	Sjogren Syndrome
Lung	Sjogren Syndrome, LIP
Skin	B. Burgdorferi

Table 2: MALT Lymphoma Common Sites and Associations.

genes which control evolution to more aggressive phenotype. However, microRNAs have not yet introduced into clinical practice.

In early-stage localized MALT lymphoma, which is refractory to antibiotic therapy, a modest dose of involved field radiotherapy (25-35 Gy) yields excellent disease control [12]. A recent analysis of data from the Surveillance, Epidemiology, and End Results database showed that radiotherapy is significantly effective in early-stage ocular and cutaneous MALT lymphomas [13]. However, inferior survival was noted in patients who underwent radiotherapy for localized pulmonary and gastric MALT lymphomas, as these locations may have occult systemic disease and may respond better to systemic therapy.

Transplantation as an option for the treatment of MALT

Given the indolent nature of the MZL as a group and good induction and salvage regimens currently available as treatment options, stem cell transplantations have not been widely used. Therefore, the role of high dose therapy autologous hematopoietic stem cell transplantation for MZL is unclear due to the paucity of data. However, autologous transplantation in patients with disseminated MALT lymphoma is feasible and can achieve durable disease free survival in relapse refractory MZL [14]. University of Nebraska published their 20 year experience with high dose chemotherapy followed by autologous transplantation in relapse refractory MZL, in this series, 14 patients in total had 56 months and 58 months of median progression-free survival (PFS) and overall survival (OS), respectively. There was a plateau of relapses after two years outpost-transplant and represented a durable treatment option for patients with refractory MZL [15].

Chemoimmunotherapy as an option for the treatment of MALT

Chemoimmunotherapy has replaced upfront therapy of many indolent lymphomas where initiation of treatment is needed. With the advent of rituximab (CD 20 antibody) has revolutionized the treatment of CD20+B cell malignancies. Chlorambucil is a nitrogen muster alkylating chemotherapy commonly used to treatment of CLL/SLL; chlorambucil has been used in indolent lymphoid malignancies and is still the standard of care for many elderly patients in Europe. The combinations of rituximab and chlorambucil have significantly improved the efficacy of single agent chlorambucil. In a study of 20 patients with low-grade ocular adnexal lymphoma treated with chlorambucil plus rituximab study, 95% of patients achieved complete response (CR) and 5% had partial response (PR) after treatment for 4 months. At a median follow-up of 56 months, only two relapses had been reported and no secondary myelodysplastic syndrome or malignancies had been reported [16].

The second-generation immunomodulatory drug, lenalidomide has shown significant activity in indolent B cell malignancies. Lenalidomide has shown significant activity in B cell malignancies and certain types of myelodysplasia with deletion 5q. The mechanism of action of lenalidomide is unclear, but it is a potent immunomodulatory, antiangiogenic, and antitumor activity, which has been demonstrated *in vitro and in vivo* lenalidomide in combination with rituximab have been investigated as treatment for relapsed NHL [17]. Lenalidomide plus rituximab was effective in patients with relapsed MZL. In a small study of indolent non-follicular NHL, 27 patients were enrolled, of whomnine had MZL histology (three MALT, four SMZL, and two NMZL). Out of the 27 patients, five patients achieved CR, and nine patients achieved PR. At a median follow-up of 13 months (range, 1-36 months), nine patients had lymphoma progression, and two patients had died. One-year OS rate and PFS rate were 92% and 78%, respectively [18]. A phase II study of single agent lenalidomide for the treatment of newly diagnosed MALT lymphoma was reported by an Austrian group [19]. Treatment consisted of 28-day cycle, which included lenalidomide 25 mg on days 1-21, with a 7-day break at the end of each 21 days. A total of 18 patients were included in the trial. Five had gastric and 13 had extra gastric MALT lymphoma, with first cycle of therapy. The overall response rate (ORR) was 61%. 11 of the 18 patients had response, six had a CR and five had PR, three patients had stable disease. The most common side effects were cytopenias and pruritus. After a median follow-up of 20.3 months, one patient had died of lymphoma, while the remaining patients did not have progressive lymphoma and were alive.

Bendamustine is a novel alkylating agent developed in East Germany in 1960s. Significant antitumor activities have been shown in broad spectrum of lymphoid malignancies. Food and Drug Administration approved this drug for the treatment of relapse indolent B-cell lymphomas, which have progressed within six months

of treatment with a rituximab base regimen. Currently, there are front-line trials of which are led by the Spanish GrupoEspañol de Linfomas/ TrasplanteAutólogo de MédulaÓsea [20] reported the results of a phase II clinical trial of bendamustine plus rituximab as first-line therapy for MALT lymphoma. Patients were treated with bendamustine (90 mg/m^2 on days 1 and 2) and rituximab (375 mg/m^2 on day 1) every 28 days. After three cycles, ORR were 100%, and 76% of patients had achieved CR. At a median follow-up of 16 months (range, 3-40 months), only one patient had died. Toxic effects were generally manageable, and the most common was neutropenic fever.

SMZL

SMZLs represent approximately 20% of MZLs [1]. Patients with SMZL usually presents with cytopenias and splenomegaly. Peripheral or bone marrow aspirate smear diagnosis of SMZL traditionally requires the morphologic presence of cytoplasmic villi and clonal lymphoproliferation, but the histologic architects can be unpredictable, as prolong storage and anticoagulants can alter the morphology of these malignant clones. SMZLs are composed of small mature B-cells in the white pulp follicles and commonly involve splenic hilar lymph nodes, bone marrow, and peripheral blood. Deletion of long arm of chromosome 7 has been extensively described in nearly half of all SMZLs [21]. There is no correlation between deletion of 7q and target genes of interest but has been noted to be helpful in diagnosis of SMZL [14].

Many groups are inclined towards molecular diagnostics in order to differentiate SMZLs from similar B-cell malignancies. HCL is a closely related disease, which may present with similar clinical features. Therefore, great interests have been generated in more objective methodology to differentiate the two diseases. One group has reported on quantitative polymerase chain reaction confirmed that BRAFV600E is 100% specific and highly sensitive (97.8%) for differentiating HCL from SMZL. The mutation for the BRAFV600E was found in 178/182 (97.8%) of HCL cases but 0/83 of SMZL cases [22]. The exact pathogenesis of SMZL is currently unknown; however, whole-exome sequencing has identified variations in several genes of the toll-like receptor/NF-κB pathway (Myd88, Peli3), B cell receptor pathway (Myd88, Arid3A), and signal transduction (ARHGAP32) pathway, all of which are essential for B-cell differentiation. These variations and others involving selected genes, such as the Bcl6 repressor (BCOR), were validated by capillary sequencing. SMZL samples contain somatic mutations involving genes regulating B cell receptor signaling, toll-like receptor/ NF-κB pathways, and chromatin remodeling [23].

Hepatitis C virus (HCV)-related SMZL is a special case in which chronic infections such HCV causes activation of the B cell receptor through E2 glycoprotein and CD81 interaction, thereby leading to lymphoproliferation [24]. Lymphomagenic effect of HCV was directly tested and proved that treatment of HCV leads to regression of lymphoproliferation and that HCV may contribute to lymphomagenesis [25].

Treatment of SMZL has been based on symptomatology, and "watch and wait" for asymptomatic patients are the standard of care. Abdominal pain and significant cytopenia can be relieved with splenectomy; however, surgical splenectomy is usually associated significant morbidity in this population [26]. Therefore a great interest in less invasive treatment option was desperately sought. Rituximab, an anti-CD20 antibody therapy has generated excitement, as majority of SMZLs express CD20, and rituximabhas are latively benign toxicity profile. Rituximab has been shown to be a reasonable first-line therapy for SMZL and is associated with less morbidity than splenectomy [27]. Rituximab produces a quick response with a high ORR and CR and negligible toxicity, but the optimal dosing treatment schedule has not yet been defined, and long-term outcomes have not yet been evaluated. Rituximab plus single agent chemotherapy (cyclophosphamide, chlorambucil or fludarabine) has been shown to be effective and tolerable [27]. The International Extranodal Lymphoma Study Group [28] has begun a phase II prospective study to assess the safety and efficacy of combination treatment with rituximab and bendamustine in symptomatic patients with SMZL, whom are not eligible for or not willing to undergo splenectomy.

NMZL

NMZL is an uncommon lymphoma and is defined as having lymph node involvement but no involvement of the spleen or extranodal sites. Disseminated disease is the most common presentation; therefore, the assessment of a potential disease evolution needs to be considered with adequate hematopathology review for more aggressive large B-cell lymphomas. NMZL usually represents a disseminated form of MALT and FL; therefore, treatment options are similar to those mentioned in MALT lymphoma. Patients present with disseminated peripheral and abdominal lymphadenopathy. Peripheral blood is rarely affected, and bone marrow involvement is seen in less than half the patients with NMZL. Morphologic examination of patients with NMZL will show that lymph node pathologies will show a spectrum of morphologies, including marginal zone-like/perifollicular, nodular, and diffuse patterns. Lymphoepithelial lesions can be seen in both reactive conditions and low-grade lymphomas such as NMZL. Both HCV infection and a serum M component have been reported to be present in NMZL cases; however, a clear association has not been established. There is no diagnostic hallmark for NMZL, and its molecular pathogenesis is still unknown. Recurrent cytogenetic abnormalities reported in the literature are +3, +7, +12, +18, and rearrangements of chromosome 1 involving two common loci in 1q21 or in 1p34 [29,30]. About three-fourths of patients with NMZL will show immunoglobulin heavy chain variable genes somatic mutations [31]. The 5-year OS rate for NMZL is 60%-70%, although no treatment consensus is reflected in the National Comprehensive Cancer Network Guidelines. For very limited-stage disease, surgery and radiation therapy may be feasible in the appropriate clinical setting [32]. Currently accepted treatment modalities of MZL are summarized in Table 3.

Novel treatment options for MZL

Bortezomib: Bortezomib a proteasome inhibitor, which has been extensively studied in plasma cell disorders and mantle cell lymphoma. The mechanism by which bortezomib affect malignant B cells is by binding to the catalytic site of the 26S proteasome, where by not allowing for degradation key pro-apoptotic and activation key proteins involved in programmed cell death. Intrials utilizing bortezomib [33,34] as single agent in relapse patients with NHL bortezomib were administered 1.5 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle. Unfortunately, the numbers of MZL cases were too few to make any conclusions; however, the studies suggest bortezomib has modest clinical activity in relapsed B-cell NHL.

Lenalidomide: Second generation immunomodulatory drug lenalidomide has shown significant promise in B cell malignancies. The mechanism is believed to modify the lymphoma microenvironment to aide in immune response and antiangiogenic effects. Given the significant activity and safety of lenalidomide, frontline studies are being conducted for indolent B cell malignancies. In MZL, the proven regimen of lenalidomide plus rituximabis being evaluated for untreated indolent lymphoma, a study of which included the largest MZL sample

size to date with 27 subjects; two-thirds of patients achieved CR, and 22% and 11% had PR and stable disease, respectively [35]. Table 2 illustrates the published data (abstracts not included) on the use of novel agents' proteasome inhibitor, immunomodulatory drugs and bendamustine in MZL.

Ibrutinib (PCI-32765): B-cell antigen receptor (BCR) signaling is implicated in the pathogenesis of B cell malignancies. Constitutive activation of BCR oncogenic signal is a validated driver of B cell neoplasms and target of treatment. Ibrutinib is a small molecule, orally bioavailable irreversible inhibitor of Bruton tyrosine kinase, which is a downstream kinase responsible for propagation of BCR signaling [36]. Initial phase I and II studies in relapsed/refractory B cell malignancies including MZL. ORR was 60% with CR of 16%. The drug was very well tolerated and showed significant clinical activity [37]. In other indolent B cell malignancies such as CLL [38] and MCL [39], phase II clinical trial data are showing Ibrutinib's remarkable activity in the relapse refractory disease. This drug is currently being fast tracked for Food and Drug Administration approval in the near future.

Veltuzumab (IMMU-106): Humanized anti-CD20 antibody that recognizes a different epitope compared to rituximab has shown activity in refractory lymphoma [40]. A multicenter phase I/II, veltuzumab dose finding study was performed in relapsed/refractory NHL [41]. Patients were given four, once-weekly doses of 80-750 mg/m^2 of veltuzumab; of the patients with MZL, five (83%) of six patients had responses, two (33%) had CR. The CRs were durable and greater than one year at the time of publication. This appears to a promising targeted agent for patients CD 20 positive MZL. Please see Table 4 for a concise summary of the clinical trial results of novel agents.

Progression of MZL

A Swiss group reported a large retrospective study that documented the risk of histologic transformation is low across all MZL types [16]. The incidence of histologic transformation in MZL is lower than other indolent B-cell malignancies, namely FL and CLL. As also observed in FL and CLL, histologic transformation in MZL occurs relatively early in clinical course, pointing to putative biological difference at diagnosis in patients with MZL destined to transformation. This clearly demonstrates the distinct biological differences between indolent B cell neoplasms and the need to conduct clinical trials which distinguishes histologic subtype instead of lumping all indolent NHLs into one group.

Conclusion

We have a better understand the biology of B cell lymphomas including

Mucosa Associated Lymphoid Tissue (MALT) Lymphoma	Nodal Marginal Zone Lymphoma (NMZL)	Splenic Marginal Zone Lymphoma (SMZL)
• Watchful waiting for favorable risk. • Gastric MALT lymphoma with H Pylori should be treated for the infection. • For non-gastric MALT lymphoma which is localized can be treated with involved field radiation therapy • t(11;18) do not respond well to single alkylating agent	• Watchful waiting for favorable risk • Systemic treatment adapted from follicular lymphoma o Rituximab alone o Rituximab plus chemotherapy	• Watchful waiting for favorable risk • Initiating treatment for SMZL includes the following : progressive or painful splenomegaly and worsening cytopenia (Hgb<10g/dl, platelets <80K/ul or ANC <100/ul • Concurrent hepatitis C virus infected patients may be treated with pegylated interferon and ribavirin. • Splenectomy can lead to significant improvement of cytopenia for patients who are eligible for surgery

Table 3: Current Treatment Options Available for MZL.

Study	N Total (# MZL)	Year	Treatment	Response Rate	PFS and OS
Sinha et al. [42]	19 (3 MZL)	2012	Bor+R+CHOP (frontline)	ORR: 100% and CR: 68	[Seems the N should be reported in the same column for each study→] (N=19) 3yr PFS:89.5% and OS: 94.7%
Gerecitano et al. [43]	57 (16 MZL)	2011	R-CBorP (salvage)	(N=57) Weekly ORR: 46% CR: 23%; Biweekly: ORR 64% CR: 36%	NR
Friedberg et al. [44]	31 (3 MZL)	2011	Bor/Bendamustine/R (salvage)	(N=31) ORR: 83%,	(N=31) 2yr PFS: 47%
O'Connor et al. [21]	77 (8 MZL)	2010	Bor single agent (salvage)	(N=77) ORR: 45%, CR: 10/77 13%	NR
Di Bella et al. [26]	60 (6 MZL)	2010	Bor single agent (salvage)	CR 1/6 (16.7%) SD 2/6 (33%) PD 3/6 (50%)	(N=60) median PFS 5.1mons (r: 0.2-22.7); 2 yr. OS: 58%
De Vos et al. [45]	18 (11 MZL)	2009	Bor(1.3mg BIW) + R vs. Bor (1.6mg QW)+R	Bor (1.3mg) MZL ORR 4/8 50% CR:	Median PFS 10.0 mons
Witzig et al. [46]	43 (3 MZL)	2009	Lenalidomide single agent (salvage)	MZL ORR: 0% SD: 2/3 66% PD: 1/3 33%	NR
Kiesewetter et al. [19]	18 (18 MALT)	2013	Lenalidomide single agent	ORR 61% (33% CR, 28% PR)	Median FU: 20.3mons
Advani et al. [37]	56 (1 MZL)	2013	Ibrutinib single agent	ORR 47% (0/1 MZL)	Median PFS: 13.6monts
Kahl et al. [35]	100 (16 MZL)	2010	Bendamustine+R (Salvage)	7 MALT lymphoma ORR 86% CR43% SD14% 9 NMZL: ORR 78% CR11% SD 22%	(N=100) median FU: 11.8mons; PFS 9.3 mon
Friedberg et al. [47]	76 (2 MZL)	2008	Bendamustine single agent (salvage)	2 MZL CR 1/2 50%; PR 1/2 50%	(N=76) Median FU: 26mons; Media PFS: 7.13 mons; OS: NR
Robinson et al. [48]	66 (2 MZL)	2008	Bendamustine +R (salvage)	(N=66) ORR 92% CR 41%	(N=66) Median FU: 20mons; Media PFS: 23 mons; OS: NR
Rummel et al. [49]	63 (6 MZL)	2005	Bendamustine single agent (salvage)	6 MZL: ORR 5/6 83%; CR 4/6 67%	(N=63) Median PFS: 24 mons
Morschhauser et al. [41]	82 (6 MZL)	2009	Veltuzumab single agent (salvage)	6 MZL: ORR 5/6 83%; CR 2/6 33%	The two CRs were ongoing at 14.6 and 26.2 mons.

Bor: Bortezomib; ORR: Overall Response Rate; CR: Complete Response; PR: Partial Response; PD: Progressive Disease; SD: Stable Disease; PFS: Progression-Free Survival; OS: Overall Survival; MALT: Mucosa-Associated Lymphatic Tissue; CHOP: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone; QW: Weekly. NR: Not Reported; r: Range; FU: Follow-up; R: Rituximab

Table 4: Novel AgentsBortezomib, Lenalidomide,Ibrutinib, Veltuzumab and Bendamustine in MZL.

MZL. Improved diagnostic ability with applications of molecular techniques, however, due to the low incidence of the disease there is a lack of strong prospective clinical trials that can set the standard of care for these patients. We are witnessing new novel target therapies that will provide patients with clinical benefit and minimize side effects. Greater need for cooperation between centers in the international setting will be needed for this field to move forward.

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