

Management of relapsed/refractory marginal zone lymphoma: focus on ibrutinib

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Abstract: Marginal zone lymphomas (MZLs) consist of a diverse family of malignancies, which are derived from B-cells. The disease subtypes are recognized extranodal, nodal, and splenic MZLs. The disease characteristics, clinical course, and treatment vary considerably based on the site of involvement. In 2017, the US Food and Drug Administration approved ibrutinib, a first in class Bruton's tyrosine kinase inhibitor that revolutionized the care of chronic lymphocytic leukemia patients; for, the treatment of relapsed/refractory MZL based on pivotal open-label Phase II trial demonstrated an overall response rate of 48%, with a complete response rate of 3%, median progression-free survival of 14.2 months, and median overall survival not yet reached at a median follow-up of 19.4 months. In this review, we aim to summarize the current conundrums in the management of MZL and the evolving role of ibrutinib in the treatment of MZL.

Keywords: non-Hodgkin's lymphoma, marginal zone, ibrutinib

Introduction

Marginal zone lymphoma (MZL) is the third most common lymphoma, accounting for 8%–12% of all B-cell non-Hodgkin's lymphomas (NHL).^{1,2} MZL originates from memory B lymphocytes harbored in the marginal zone of secondary lymphoid follicles present in the spleen, mucosa-associated lymphoid tissues, and rarely lymph nodes.³ The development of MZL is associated with chronic antigen-mediated B-cell receptor (BCR) activation in most cases.^{4–7} The Surveillance, Epidemiology, and End Results (SEER) data have shown that MZL occurs in adults with a median age of 67 years, but with a slight female predominance.^{8–10} Based on the involved sites and characteristic molecular findings, the World Health Organization classified MZL into 3 specific subtypes, each with its own unique epidemiology, clinical presentation, and therapeutic options.¹ These subtypes include extranodal marginal zone lymphoma (EMZL), also called mucosa-associated lymphatic tissue (MALT) lymphoma; splenic MZL (SMZL); and nodal MZL (NMZL).¹

Over the past 5–7 years, a greater understanding of the disease biology, including genetic and molecular characterization, has changed the therapeutic landscape of MZL. Novel pharmaceutical engineering approaches focusing on intracellular signaling pathways have resulted in targeted therapies that have improved efficacy and tolerable toxicity profiles. There has been a growing evidence on the role played by the BCR signaling pathway in the pathogenesis of B-cell lymphoproliferative disorders, including MZL.^{11–13} In many of these malignancies, small molecule kinase inhibitors targeting BCR signaling, such as the Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib), seem

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to provide new avenues of therapeutic strategies.¹² Here, we provide a brief overview of the various subtypes of MZL, discuss in detail the management of MZL, and focus on the emerging role of ibrutinib in this realm.

MZL – a heterogeneous disease entity: epidemiology and presentation

EMZL

Epidemiology of EMZL

EMZL, also called MALT lymphoma, is the most common subtype of MZL, accounting for ~70% of all MZLs.¹⁴ Median age at diagnosis is 50–60 years.¹⁵ EMZL can originate at virtually any extranodal site and arises in organs that normally lack lymphoid tissue (eg, stomach, intestine, thyroid, lung, and skin). Pathogenesis of EMZL involves continued proliferation of B cells and persistent stimulation of the BCR signaling pathway. The latter seems to be induced by chronic inflammation^{16–21} as a result of both infectious and autoimmune causes. Examples of infectious and EMZL correlative relationships include gastric EMZL arising from *Helicobacter pylori*, MZL localized to the skin and *Borrelia burgdorferi*, the ocular adnexa and *Chlamydia psittaci*, the small intestine and *Campylobacter jejuni*, and possibly the lung with *Achromobacter xylosoxidans*. The most frequently affected organ in EMZL is the stomach, and there is compelling evidence for a causal relationship between *H. pylori* and gastric EMZL.^{5–7,22} Chronic hepatitis C viral (HCV) infection has been implicated in the pathogenesis of all MZL subtypes^{21,23–26} and mainly affects the non-gastric sites, often the salivary or lacrimal glands in EMZL. Autoimmune diseases also increase the risk of non-gastric EMZL at various anatomical sites; for example, primary Sjogren's syndrome results in a greatly increased risk for salivary gland EMZL, and Hashimoto's thyroiditis has been implicated in the development of thyroid EMZL.^{27–31}

Presentation of EMZL

EMZL most commonly presents as extranodal disease and is limited to the site of origin (Ann Arbor stage IE); peripheral lymph node and bone marrow (BM) involvement is uncommon.³² Diagnosis is made by tissue biopsy, with confirmation of diagnosis by an expert hematopathologist to avoid overtreatment of benign reactive conditions or other lymphoma entities.³³ Clinical signs and symptoms of EMZL may vary according to the site of primary location.³³ Gastric EMZL is most common, accounting for one-third of all sites of localization and frequently presents with early-stage localized

disease, while disseminated disease is more common with primary non-gastric sites.^{34–38}

SMZL

Epidemiology of SMZL

SMZL arises predominantly from the marginal zone memory B-cells located in the follicles of the spleen, splenic hilar lymph nodes, BM, and the peripheral blood.³⁹ SMZL accounts for ~20% of all MZLs,^{1,40} and the median age of occurrence is 69 years.⁴¹ The pathogenesis of SMZL has yet to be fully understood; similar to other subtypes of MZL, it likely involves the persistent stimulation of BCR signaling pathway, with increasing proliferation and survival of malignant B cells.¹³ Though the association between HCV infection and SMZL has been described, there seems to be some geographic difference given the variation in seroprevalence from one series to the other.^{42–44}

Presentation of SMZL

Most SMZL patients are asymptomatic at the time of presentation with anemia, thrombocytopenia, or lymphocytosis incidentally found on routine blood test. Subsequent referral to the hematologist and further workup then may reveal SMZL. Advanced stage SMZL, however, can present with massive splenomegaly, abdominal pain, and early satiety. Symptomatic cytopenias may be present, and imaging may show splenic hilar lymphadenopathy.⁴⁵ Up to 20% of patients also present with autoimmune manifestations, including hemolytic anemia, immune thrombocytopenia, and acquired coagulation disorders.^{42,46} Definitive diagnosis can be made from histopathologic evaluation of the spleen, which shows a nodular lymphoid proliferation with a biphasic appearance effacing the white pulp, involving the red pulp in a patchy fashion, and infiltrating the vessel wall. If histopathologic evaluation of the spleen is unavailable, diagnosis can be made by immunophenotyping of peripheral blood cells coupled with the histopathologic evaluation of the BM showing intrasinusoidal infiltration of CD20+ cells.^{1,47,48}

NMZL

Epidemiology of NMZL

NMZL is the least common subtype of MZL, representing <2% of all NHL and ~10% of all MZLs.¹ The median age of patients diagnosed with NMZL is between 50 and 60 years.⁴⁹ The molecular pathogenesis of NMZL is still incompletely described but likely involves constitutive BCR signaling, resulting in proliferation and survival of malignant B cells.⁵⁰

Presentation of NMZL

Similar to other indolent nodal lymphomas, such as small lymphocytic lymphoma and follicular lymphoma (FL), the majority of patients with NMZL present with non-bulky disseminated peripheral, abdominal, and thoracic lymph node involvement.^{51,52} B symptoms are rare, and diagnosis requires exclusion of splenic and other organ involvement to distinguish it from other subtypes of MZL. Though involvement of BM can occur in about one-third of patients, peripheral blood involvement and cytopenias are rare.^{51,53}

Management of MZL

Frontline treatment of MZL

Frontline therapy for MZL differs greatly based upon the subtype and underlying etiology. For example, a significant proportion of patients with HCV and EMZL will note regression of the lymphomatous process after undergoing antiviral treatment for HCV infection.^{24,26,54–60} Thus, antiviral therapy for HCV is recommended for all cases of MZL associated with HCV infection.

EMZL

In patients with gastric EMZL that are positive for *H. pylori*, antibiotics targeting *H. pylori* are the initial treatment of choice. With documented *H. pylori* eradication, the majority of *H. pylori*-positive patients (up to 75%) will go into remission.⁶¹ However, ~50% of patients with gastric *H. pylori*-positive EMZL will have relapse/progressive disease with antibiotic therapy alone^{62,63} and require further therapy. A smaller proportion of *H. pylori*-negative gastric EMZL patients and those with non-gastric EMZL (with or without a known causative microbial agent) will respond to antibiotics alone. Hence, it is reasonable in most patients to attempt antibiotic therapy as a first-line therapy; however, most will require alternative and subsequent therapy.^{64–70} Though detailed guidelines for response assessment and follow-up have been published,³³ there are no consensus guidelines with regard to the optimal second-line treatment after initial therapy failure.^{35,37,38,71} Involved-field radiotherapy (IFRT) (dose of 25–35 Gy) is a reasonable first-line (in *H. pylori*-negative cases) or second-line option (in *H. pylori*-positive cases who fail *H. pylori* eradication therapy) for patients with localized disease, providing excellent local disease control, though distant failures still occur.^{72–77} Rituximab can be used alternatively if IFRT is not possible. With disseminated gastric or non-gastric disease, observation may be an adequate initial approach.

In patients who require systemic treatment, various combinations have been used and studied. The 2013 StiL trial looked at previously untreated indolent lymphoma and compared the standard of therapy, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), to a combination of bendamustine plus rituximab.⁷⁸ They found that compared with R-CHOP, the combination of bendamustine and rituximab (BR) had increased progression-free survival (PFS), and there were fewer adverse events (AEs).⁷⁸ Salar et al subsequently investigated BR specifically in EMZL and had good outcomes.⁷⁹ Thus, historically for EMZL, bendamustine plus rituximab have been used as an active and well-tolerated first-line treatment.⁷⁹ More recently, the final results of the randomized multicenter IELSG-19 trial were published.⁸⁰ This randomized trial focused specifically on frontline therapy for EMZL and included 3 arms: chlorambucil monotherapy, chlorambucil plus rituximab, and rituximab monotherapy.⁸⁰ What they found was that, between arms, overall survival (OS) was without significant difference.⁸⁰ However, the chlorambucil plus rituximab arm did provide significantly improved event-free survival (EFS) and PFS,⁸⁰ and thus, the combination of rituximab with chlorambucil has gained traction as the initial treatment of choice for EMZL.

SMZL

Asymptomatic patients with SMZL can undergo observation for multiple years with routine clinical examinations and blood counts; observation in these patients does not influence overall outcomes.^{81,82} Based on the consensus guidelines, treatment for SMZL is only indicated for symptomatic splenomegaly, progressive nodal disease, symptomatic cytopenias, and/or autoimmune cytopenias.^{47,55,59} Initial treatment options include splenectomy, rituximab alone, and chemotherapy combined with rituximab.^{83–88} Conventionally, initial treatment for patients with symptomatic splenomegaly and/or cytopenias secondary to splenic sequestration was splenectomy, and patients could remain disease-free for many years after the surgery.^{42,81,82,89,90} More recently, rituximab-based therapy has become a first-line alternative to splenectomy with outcomes comparable with or better than splenectomy.^{55,59,84,86,91–94} A combination of rituximab and chemotherapy is indicated for those with disseminated disease, constitutional symptoms, and/or having signs of high-grade transformation.^{55,59}

NMZL

There are no treatment guidelines focusing specifically on NMZL. Treatment and management typically follow that of

similarly staged FL.⁵⁹ In localized disease, targeted radiotherapy is appropriate, while in both limited and advanced-stage diseases with low tumor burden, watchful waiting is employed. No trials to date have looked at NMZL specifically; however, with more advanced-stage disseminated disease requiring treatment, immunochemotherapy regimens comprising rituximab plus chemotherapy with or without an anthracycline are typically used.

Management of relapsed/refractory (R/R) MZL

Treatment for R/R MZL is similar to that of advanced stage or disseminated MZL. It is typically approached in a manner similar to other indolent B-cell lymphomas, such as FL.⁵⁵ Unfortunately, patients with MZL are often excluded from larger studies of more common indolent B-cell lymphomas, and thus, no disease-specific treatment guidelines have been developed.¹² Only smaller disease-specific trials have been performed and must be used in conjunction with extrapolation from larger studies in which MZL was included to assist with optimization of treatment choice.

Across MZL subtypes, if no prior immunochemotherapy has been received, various regimens combining rituximab and chemotherapy-containing regimens have classically been the initial treatment of choice, resulting in overall response rate (ORR) of 85%–93% and complete response rate (CR) of 54%–78%.^{80,95–98} Grade III–IV myelosuppression is common with these regimens and may exclude some patients from eligibility for these therapies.¹²

Autologous and allogeneic hematopoietic progenitor cell transplantation (HCT) has been performed in selected patients with R/R MZL, achieving durable remissions and frequently cures, albeit at cost of significant morbidity.^{99,100} Though standardized guidelines for selecting R/R MZL appropriate for HCT are lacking due to a paucity of data,^{101–103} HCT can be utilized with excellent outcomes in selected fit patients having aggressively behaving disease.^{99,100} Autologous transplant is usually indicated in fit patients with transformation to aggressive lymphoma. Chimeric antigen receptor-modified T-cells have consistently demonstrated activity in advanced hematologic malignancies, including different types of lymphomas, and clinical trials are underway in patients with various types of indolent B-cell lymphomas (including MZL).¹⁰⁴

R/R EMZL

The optimal treatment of R/R EMZL remains to be defined. For patients who have progressed after local therapy,

single-agent rituximab or multiple rituximab-based chemotherapy combinations are usually employed. In the IELSG19 study, the combination of rituximab with chlorambucil resulted in superior EFS and PFS compared with rituximab and chlorambucil monotherapy. However, this study focused on first-line therapy; only 8% of patients were enrolled after treatment failure, and OS was similar in both groups.⁸⁰ Thus, though further investigation into the combination of chlorambucil and rituximab, if not previously used, may be warranted, for patients failing locally therapy, single-agent rituximab is still the preferred first option.⁸⁰ BR regimen has gained popularity in the US for excellent tolerance and superior outcomes in other indolent B-cell lymphomas.¹⁰⁵ ORR of 93% has been achieved in patients with R/R EMZL (CR 71%) with the BR regimen with durable remissions at a cost of 29% incidence of Grade III–IV hematological toxicity.¹⁰⁶ The proteasome inhibitor bortezomib also has significant single-agent activity in R/R EMZL with an ORR of 48% (CR 31%).¹⁰⁷ Similar impressive results were noted when bortezomib was combined with rituximab in R/R MZL.¹⁰⁸ ORR of up to 80% (with 54% CRs) were also reported with the combination of rituximab with the immunomodulating agent lenalidomide, with no unexpected toxicities.¹⁰⁹

R/R SMZL

R/R patients with SMZL include those who failed local treatment (splenectomy) and those progressing on rituximab monotherapy. Though rituximab-based chemotherapy combinations can be employed in this setting,^{55,59} treatment, or retreatment in patients who previously receiving rituximab monotherapy is a commonly employed and retains its efficacy in most cases.^{110,111} BR has also gained popularity as a preferred regimen in R/R SMZL based on the impressive ORR (92%) observed in the BRIGHT study in MZL patients (n=25).¹¹²

R/R NMZL

Though no studies have specifically looked at R/R NMZL, strategies comparable with similarly staged FL are used, and combination therapies with immunochemotherapy are most typical.⁵⁰ Good outcomes have been seen in some studies with bortezomib in particular, which has shown promising activity specifically when looking at NMZL.^{107,113,114}

Prognosis of MZL

EMZL

The natural history of EMZL is indolent, and SEER analysis shows 5-year OS rate of 88.7% and median OS 12.6 years.¹⁰ Median time to progression is better for GI compared with

non-GI EMZL;⁷⁴ however, GI and pulmonary involvement had a worse survival compared with other locations, with a 5-year incidence rate of lymphoma-related death of 9.5%–14.3% compared with 4.5%–7.8%, respectively.¹⁰ For patients not responding to antibiotics, with Stage IE–IIE EMZL treated with IFRT only, OS at 10 years is 79%–87%.^{74,75} Outcomes for high-dose systemic therapy/autologous hematopoietic stem cell transplantation in disseminated EMZL are similar to those in FL.^{102,103} Enrollment in clinical trials is highly encouraged given the limited therapeutic options in R/R EMZL.¹⁰¹ Despite frequent relapses, EMZL often maintains a relatively indolent course.³⁵ Relapses most commonly occur in the tissue of origin; however, involvement of other sites (including lymph nodes) can occur.¹¹⁵ Using the data from IELSG-19 trial, Thieblemont et al reported MALT-IPI (International Prognostic Index) as a prognostic tool for risk stratifying patients with MALT. Patient who were ≥ 70 years, with advanced stage (Ann Arbor Stage III or IV) and elevated lactate dehydrogenase (LDH) conferred poor outcomes in EMZL patients. Based on the presence of 0, 1, and 2 or more risk factors, the patients were stratified into low-, intermediate-, and high-risk groups.¹¹⁶

SMZL

Though the majority of SMZL run an indolent course similar to EMZL, overall, SMZL has poorer outcomes due to a relatively larger proportion of patients who present with aggressive disease.¹¹⁷ The median OS for SMZL is ~8–10 years;^{10,43} however, in cases of aggressive disease (~25%–30% of cases), the median survival is <4 years.^{43,117} In SMZL, the Italian Foundation of Lymphomas prognostication index can be used to risk stratify patients by presence of risk factors, including low hemoglobin, elevated LDH, and reduced albumin level at diagnosis. The 5-year disease-specific survival rate was 88% in the low-risk group, 73% in the moderate-risk group, and 50% in the high-risk group.⁴³ Subsequently, other prognostic models were also developed^{118,119} to optimize prognostication and can therefore be used. However, these models are based on clinical parameters and are not 100% sensitive or specific. Hence, incorporation of mutational/genetic markers into the current clinical prognostic models may be required in the future to improve risk stratification of SMZL patients.

NMZL

The overall prognosis for NMZL is worse than EMZL when presenting as disseminated disease¹²⁰ and more comparable with SMZL and other indolent lymphomas.^{10,50,121} To date,

this disease remains incurable and is characterized a pattern of recurring relapse at nodal sites.⁵⁰ With the advent of newer therapies, the average 5-year OS of NMZL has reached 70%–90%.¹²² Both the IPI and the FL International Prognostic Index are used in NMZL to stratify patients into high and low risk.^{50,122}

Role of ibrutinib in MZL – is it ready for primetime?

The importance of the role played by BCR signaling in the development of MZL cannot be undermined.^{11,13} BTK plays a key role in the BCR signaling pathway and has been shown to be involved in the formation, survival, and proliferation of malignant B cells.^{123–126} The efficacy of Food and Drug Administration (FDA)-approved ibrutinib in other lymphoid malignancies, including chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle cell lymphoma, and Waldenström's macroglobulinemia is well known.¹² Given the likely importance of BCR, induced by chronic antigenic stimulation, in the development of MZL,⁴ it was theorized that BTK targeting may play a role in therapy for R/R MZL. A Phase I trial of single-agent ibrutinib in 56 patients with heavily pre-treated B-cell malignancies (median number of prior therapies =3) included 4 patients with R/R MZL; 1 patient sustained a partial response and 3 had stable disease,¹²⁷ thus opening the window for further studies.

Subsequently, a pivotal, Phase II open-label international study was conducted using ibrutinib in patients with R/R MZL previously treated with rituximab-based therapy.¹² The study included 60 evaluable patients who were treated with single-agent ibrutinib (560 mg orally daily) administered until progression or unacceptable toxicity. ORR was 48% and median PFS was 14.2 months. CR was noted in 2 patients (3%). Progression of disease was the main reason for treatment discontinuation, occurring in 32% of study participants. Though AEs occurred in 44% of patients, the rates of treatment discontinuation and dose reduction due to AEs were relatively low at 17% and 10%, respectively. These were comparable with rates of discontinuation due to AE seen in other similar studies with ibrutinib. At a median follow-up of 19.4 months, 38% still remained on ibrutinib, and median OS has not been reached.

Outcomes were also analyzed by MZL subtype. Median PFS was 13.8 months for EMZL, 19.4 months for SMZL, and 8.3 months for NMZL. Estimated 18-month OS rate was 81%, and of the 8 patients who died during the study, 4 (7%) were attributable to progression of disease. At the time, this study was published (19 months from start date),

the median duration of response has not yet been reached. Overall, the rate of disease control based on clinical benefit was 83%, and 78% of patients were shown to have reduced tumor burden. Clinical response to ibrutinib was seen in all subtypes. Response occurred in those treated with prior chemotherapy, immunotherapy, or a combination of the two. Responses were seen in both relapsed and refractory patients as well as those with bulky disease and/or BM involvement.¹²

Based on these results, FDA granted accelerated approval for ibrutinib for the treatment of R/R MZL requiring systemic therapy and progressing on at least 1 prior anti-CD20-based therapy. It is noteworthy that, prior to ibrutinib, no therapeutic agent had been approved by the FDA specifically for treatment of MZL. Currently, ibrutinib provides a viable alternative treatment option to chemoimmunotherapy for the treatment of R/R MZL.¹²

Compared with MZL, ibrutinib has shown only modest activity in FLR/R FL. A recent Phase II consortium trial of 40 patients with R/R FL has shown ORR of 37.5% with CR of 12.25, median PFS of 14 months, and 2-year PFS of 20.4%. Response rates were significantly higher among patients whose disease was sensitive to rituximab (52.6%) compared with those who were rituximab refractory (16.7%). CARD11 mutations were present in 16% (5/31) of patients and predicted resistance to ibrutinib.¹²⁸ This is in contrast to an ORR of 82% with CR 27% in untreated FL in the Phase II PCYC-1125-CA study that included 80 patients, with the majority having Stage III/IV disease. In that same trial, the median PFS and OS has not been reached as only 5 patients had disease progression.¹²⁹ Ibrutinib was well-tolerated in both trials with low incidence of AEs.

Combination therapies that include BTK inhibition as well as other agents are currently ongoing and have much potential. Currently, a randomized, double-blind, multicenter Phase III trial, SELENE, is underway. This trial is investigating ibrutinib vs placebo in combination with either BR or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients with previously treated MZL or FL (NCT01974440). The primary objective is to determine whether ibrutinib vs placebo in combination with BR or R-CHOP will prolong PFS, with secondary objectives, including OS, CR, ORR, safety, and toxicity.¹³⁰ With the advent of novel combination approaches with more tolerable side effects and improved efficacy, there is hope that optimal and standardized treatment regimens for MZL may soon be around the corner. Ibrutinib is also being investigated in combination with lenalidomide ± rituximab (NCT02532257 and NCT01955499); selinexor (KPT-330), a selective inhibitor

of nuclear export (NCT02303392); the check point inhibitor pembrolizumab (NCT02332980); and other target agents in R/R MZL and other B-cell malignancies.

Future directions

In the current landscape, standardized treatment algorithms still lack sufficient evidence-based guidelines required to guide optimal therapy. Obinutuzumab, which has shown efficacy in FL, is currently being tested both in combination with chlorambucil and bendamustine in current Phase III trials for MZL.^{131,132} However, Herold et al recently reported the results of a subset of patients in the randomized Gallium trial comparing obinutuzumab or rituximab in patients with previously untreated advanced stage MZL.¹³³ This study did show a significant difference in PFS between arms and actually showed increased frequency and severity of AEs.¹³³ Other investigatory trials continue to be underway looking for other efficacious novel agents.

Conclusion

MZL is a relatively rare and heterogeneous malignancy of B-cells that makes dedicated clinical trials difficult to perform and for which standardized treatment regimens are unfortunately lacking. Though each subtype has a unique initial treatment strategy based on limited-stage disease characteristics, with more advanced stage disease and R/R MZL, regimens used for advanced FL are usually employed. Though smaller studies have specifically looked at chemoimmunotherapy regimens for R/R MZL, consensus evidence-based guidelines on treatment specific to MZL are lacking. A recent pivotal Phase II trial has shown that single-agent ibrutinib is both a safe and efficacious treatment for all subtypes R/R MZL. Based on this, ibrutinib is rapidly gaining popularity as an agent of choice in MZL that progresses after rituximab-based therapy. Future studies will inform about the role of single-agent ibrutinib in both treatment-naïve patients, and its role in R/R MZL in combination with other agents.

Disclosure

The authors report no conflicts of interest in this work.

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