Effective management strategies for patients with marginal zone lymphoma

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Marginal zone lymphoma (MZL) is an uncommon indolent lymphoma classified into subtypes based on primary site of involvement: splenic, nodal and extranodal. MZLs' relative rarity has largely precluded adoption of a standard management strategy. Here, we provide an overview of the epidemiology, clinical behavior and therapeutic approaches for each subtype. Biologic insights into lymphomagenesis have identified B-cell receptor signaling as a rational therapeutic target. Recent clinical data suggest that novel agents targeting this pathway, including the Bruton's tyrosine kinase inhibitor, ibrutinib, show significant promise in treatment of relapsed MZL. More work is needed to evaluate these agents' activity in the front-line setting, possible combination regimens and the impact of resistance to B-cell receptor-targeted agents in order to optimize therapy in MZL.

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Marginal zone lymphomas (MZLs) represent a group of uncommon hematologic malignancies that are indolent in clinical behavior, so named because they are thought to arise from memory B lymphocytes in the marginal zone of lymphoid tissue. MZLs comprise about 5–17% of all non-Hodgkin lymphomas (NHL) in adults [1] and share common immunophenotypic markers, including CD19, CD20 and CD22; typically, they are negative for CD5, CD10 and CD23 [2]. WHO classifies MZL into three subtypes depending on the site of involvement: splenic MZL (SMZL), nodal MZL (NMZL) and extranodal MZL (EMZL) or mucosa-associated lymphoid tissue (MALT) lymphoma [2]. In a large, multinational epidemiology study investigating risk factors for MZL, investigators from the International Lymphoma Epidemiology Consortium (InterLymph) found that B-cell-activating autoimmune conditions, hepatitis C virus seropositivity, self-reported peptic ulcers, asthma, family history of NHL or hematologic cancer, permanent hair dye use, and occupation as a metalworker were associated with increased risk of one or more subtypes of MZL [3]. A two-stage genome-wide association study of 1281 MZL cases and 7127 controls of European ancestry identified two independent loci near *BTNL2* and *HLA-B* significantly associated with MZL susceptibility, providing the first evidence that genetic variation in the major histocompatibility complex influences MZL risk [4]. In addition to a complex interplay of genetics and environmental exposures, the three subtypes of MZL vary in terms of their epidemiology, clinical behavior and treatment. Here we provide an overview of each subtype, first-line therapies and management strategies for relapsed/refractory MZL in adult patients.

Extranodal MZL

EMZLs are defined by involvement of nonlymph node sites and are commonly referred to as MALT lymphomas. MALT lymphoma represents the most frequently diagnosed MZL subtype, accounting for 50–70% of MZLs and 7–8% of all NHL [1]. Given the propensity for this subtype to involve the GI tract, MALT lymphomas can be further subdivided into gastric and nongastric subtypes. As in other MZL subtypes, there is a significant association between chronic antigenic stimulation, either by autoantigens or microbial pathogens, and increased risk of MALT lymphoma. Although certain autoimmune disorders have been increasingly recognized as risk factors for NHL, overall, there are few large-scale systematic assessments of risk of NHL subtypes. One notable exception is the InterLymph Consortium study that assessed association of individual autoimmune conditions with NHL subtypes, including MZL [5]. In that analysis, a diagnosis of Sjögren's syndrome resulted in a 30-fold increase in the

risk of MZL, based on 11 EMZL patients, three NMZL patients and one patient with undetermined (nonsplenic) MZL. Among patients with lymphoma of known anatomic site, ten were parotid gland EMZL, corresponding to a 1000-fold risk of parotid gland MALT lymphoma (OR: 996; 95% CI: 216–4596). Systemic lupus erythematosus was associated with a 7.5-fold increase in MZL risk, based on ten patients, seven of whom had MALT lymphoma (OR: 12.9; 95% CI: 4.91–33.8). Moreover, specific pathogens are associated with EMZLs involving certain anatomical sites: *Helicobacter pylori* for stomach MALT lymphoma [6], *Chlamydia psittaci* for ocular adnexal MALT lymphoma, *Borrelia burgdorferi* for cutaneous MZL, *Campylobacter jejuni* for small intestine MALT lymphoma [7] and *Mycobacterium* species for bronchus MALT lymphoma [8]. As mentioned above, hepatitis C viral infection can be associated with all MZLs [9]. In terms of genetic aberrations, gastric MALT lymphomas commonly harbor the chromosomal translocation t(11;18)(q21;21), which results in formation of the fusion protein AP12/MLT1. This protein product activates the NF- κ B pathway to allow avoidance of apoptosis, is associated with poor MZL response to *H. pylori* eradication, and is predictive of resistance to oral alkylating agents [10].

Clinical presentation for MALT lymphomas often correlates with location of the tumor. MALT lymphomas involving the GI tract may present with symptoms such as nausea, vomiting, abdominal pain, dyspepsia and gastric bleeding. Nongastric MALT lymphomas such as those involving lung, thyroid, salivary glands, skin, orbit, or breast may also exhibit localized signs and symptoms. Since MALT lymphomas often behave indolently, patients may not experience any symptoms at time of diagnosis, which may be made incidentally on a study for an unrelated problem (e.g., during upper endoscopy for workup of gastroesophageal reflux disease). The indolent behavior of MALT lymphomas is commonly associated with a good performance status and absence of either B symptoms or poor prognostic factors such as elevated LDH or β 2 microglobulin level.

In most cases, disease is localized at initial diagnosis; 30–40% of patients have multifocal lesions at presentation and disseminated disease (such as bone marrow or liver involvement) at diagnosis occurs in a third of MALT lymphoma patients. In a retrospective study, dissemination at diagnosis did not influence outcome after treatment. The estimated overall survival (OS) rates for localized and disseminated disease at diagnosis were the same, with 86% 5-year OS and 80% 10-year OS [11].

First-line treatment

There is currently no standard first-line treatment for MALT lymphoma, and treatment is often tailored to the individual patient. For localized MALT lymphomas involving microbial pathogens, eradication of the pathogen can cause regression of the lymphoma. For gastric MALT patients who are positive for *H. pylori* without any evidence of submucosal invasion or t(11;18), antibiotics alone can be an effective first-line therapy and provide an excellent long-term outcome. In a large multicenter study in Japan, eradication of *H. pylori* in patients with localized gastric MZL without deep mucosal invasion or t(11;18) resulted in a histological response in 77% of patients [12]. The long-term follow-up ranged from 3 to 14.6 years, with a probability of freedom from treatment failure after 10 years of 90% and 10-year OS of 95%.

For patients with gastric MALT lymphoma without *H. pylori* infection or who do not respond to antimicrobial therapy, reasonable treatment alternatives include radiotherapy, oral alkylating agents such as cyclophosphamide and chlorambucil, and/or rituximab (R) [13]. A 1995 study of MALT lymphoma patients treated with either cyclophosphamide or chlorambucil showed a 75% complete response (CR) rate following a median duration of treatment of 12 months [14]. Subsequent studies of various agents and combinations have mostly been small, and randomized trial data are limited. Two exceptions to this include the International Extranodal Lymphoma Study Group's (IELSG) study of chlorambucil versus R plus chlorambucil, which showed improvement in 5-year event-free survival (EFS; 68 vs 50%; $p = 0.002$) and a higher CR rate (78 vs 65%; $p = 0.025$) in the R-containing arm [15] and a randomized study on watch-and-wait versus chlorambucil in patients with gastric MALT lymphoma after *H. pylori* eradication [16]. Intriguingly, the latter study did not show a benefit for single-agent chlorambucil following bacterial eradication. Unfortunately, gastric MALT patients with t(11;18) have been found to be resistant to *H. pylori* treatment and are poor responders to alkylating agents, highlighting t(11;18) as a negative predictive factor for which alternative first-line treatment may need to be considered [10].

More generally, for MALT lymphoma patients who fail to respond to antimicrobial treatment or do not have an associated infection, conventional oncologic modalities for indolent lymphomas are considered, with treatment strategy depending on site, stage of disease, and performance status of each individual patient. For localized disease, radiation therapy is often a preferred option. Excellent clinical outcomes have been reported in stage I and II MALT lymphoma treated with involved field radiation, with one report demonstrating 98% 5-year OS

and 77% 5-year disease-free survival in this setting [17]. Such studies show that radiation alone can be effective in controlling localized MALT and is curative in some instances. A retrospective multicenter study of patients with gastric MALT lymphoma demonstrated that most patients treated with radiation were cured, with a 10-year freedom from treatment failure rate of 88% and 10-year OS of 70% [18]. Accordingly, guidelines from the National Comprehensive Cancer Network (NCCN) currently recommend involved field radiotherapy for stage I and II MALT lymphomas that have failed antibiotic therapy or are not infection-associated [19]. The NCCN guidelines also mention surgery as an option for management of localized disease, but this is less commonly performed given the paucity of data on its long-term effectiveness and the favorable long-term outcomes associated with radiation. When radiotherapy is not an option, R monotherapy is recommended.

The IELSG conducted a Phase II study evaluating the efficacy of 4 weekly doses of R in untreated and previously treated patients with MALT lymphoma. Overall response rate (ORR) was 73%, with 15 patients experiencing CR and ten achieving partial response (PR); median duration of response was 10.5 months. The most common adverse events were infusion-related side effects that occurred with the first infusion and were mild to moderate. This demonstrated that R as a single agent was not only effective in treating MZL, but also safe [20]. Additional trials evaluating its benefit in conjunction with chemotherapy have also been conducted. In a study evaluating the safety and efficacy of R in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for follicular lymphoma (FL; $n = 25$) and other low-grade NHL patients ($n = 15$), the ORR was 95%; 55% achieved a CR and 40% achieved a PR. Of note, the subtypes of low-grade lymphoma were not specified further in the manuscript describing these results. Thus, response rates for MZL alone were not reported, but as in many other instances, that seminal study's findings have been extrapolated to the MZL setting. The most common adverse events were alopecia, neutropenia and fever. There were also infusion-related side effects with the first infusion of R [21,22].

For patients with advanced stage MALT lymphomas, R in combination with chemotherapy should be considered, following approaches developed for patients with FL. In a Phase II study, safety and activity of R in combination with bendamustine as front-line treatment in patients was evaluated [23,24]. The primary end point was 2-year EFS. Of 57 evaluable patients, 100% achieved a CR at the end of treatment. EFS was 93% at 2 years and 88% at 4 years. In the 60% of patients who experienced grade 3–4 adverse events, most toxicities were hematological and not life-threatening. This study demonstrated that R in combination with bendamustine is safe and effective as first-line treatment for patients with MZL of any stage who are chemotherapy naïve, do not harbor chronic infections, and/or are nonresponders to anti-*H. pylori* treatment.

Splenic MZL

SMZL is defined by involvement of the spleen, bone marrow, and sometimes peripheral blood without other nodal or extranodal sites of disease. This rare subtype accounts for less than 1% of NHL and 20% of MZLs and usually affects middle-aged to elderly patients, with a median age of approximately 65 years. Splenomegaly without lymphadenopathy continues to be the hallmark clinical presentation for SMZL, with 95% of patients with SMZL demonstrating bone marrow and blood involvement [25]. Indeed, patients with SMZL often present with lymphocytosis and cytopenias such as anemia and/or thrombocytopenia. Diagnosis is suggested when there is splenic, bone marrow and/or peripheral blood involvement by small lymphoid cells with immunoglobulin light chain restriction and negativity for CD5, CD10 and cyclin D1 markers [25]. Often, however, a definitive diagnosis requires splenectomy since bone marrow morphologic features and immunophenotype may be nonspecific. The WHO classification further subdivides SMZL according to histologic absence or presence of villous lymphocytes, cells displaying short villous projections with a polar orientation, in the peripheral blood. Whether splenic lymphoma with villous lymphocytes represents a leukemic variant of SMZL remains controversial [25,26]. SMZL can be associated with autoimmune disorders, the most common of these being autoimmune hemolytic anemia and immune thrombocytopenia. Other autoimmune disorders such as systemic lupus erythematosus, Sjögren's syndrome, and rheumatoid arthritis have also been associated with SMZL [27]. Additionally, SMZL is often associated with chronic antigenic stimulation related to an infection such as hepatitis C virus.

First-line treatment

As is the case for many indolent lymphomas, timing of therapy initiation in SMZL depends on the clinical presentation. For patients with asymptomatic splenomegaly without cytopenias, B symptoms and/or autoimmune manifestations, close observation without treatment is a reasonable strategy. In fact, some patients are reported

to have been observed for 10 years with stable disease (SD) [26]. Once a patient meets criteria for initiation of treatment, there is currently no standard of care for the therapeutic approach. When the lymphoma is associated with chronic antigenic stimulation related to an infection such as hepatitis C virus, antiviral treatment has been associated with a decrease in lymphocytosis and splenomegaly, and may be considered for first-line therapy [28]. Newer treatments for hepatitis C that are less intensive and more effective than previous regimens may make this a more attractive approach in the future. Lymphoma-directed therapy is indicated when a patient presents with symptomatic splenomegaly, cytopenias, B symptoms and/or autoimmune manifestations such as hemolytic anemia. Prior to the R era, splenectomy was commonly used as a first-line therapy for patients with symptomatic SMZL. However, due to the significant morbidity associated with this abdominal surgery, this may not be a reasonable option, especially in nonoptimal surgical candidates such as the elderly or patients with multiple comorbidities. Currently, patients with SMZL who exhibit splenomegaly alone or minimal disease burden are more commonly treated with single-agent R instead. R is generally associated with limited toxicity, making it ideal for the nonsurgical candidate. In a study comparing the efficacy and safety of R monotherapy to splenectomy as front-line treatment for patients with SMZL, the 5-year OS for R-treated patients was 92%, with a 5-year progression-free survival (PFS) rate of 77%; in splenectomized patients, the 5-year OS was 73% and 5-year PFS was 58% [29]. This study demonstrated that R is effective and well tolerated in this setting, establishing it as a first-line treatment of choice for SMZL patients with low disease burden.

Patients who present with a more extensive disease or symptom burden, relapse after splenectomy, or are not good candidates for splenectomy may benefit from combination regimens with R and chemotherapy [20]. In a prospective study of SMZL patients ($n = 70$), patients who received treatment with R as monotherapy or in combination with chemotherapy were found to have a better OS and failure-free survival compared with patients who received chemotherapy alone [30]. The ORR for chemotherapy alone was 55%, compared with 83% for R + chemotherapy and 88% for R alone. Three-year OS and freedom from relapse rates also compared favorably, at 55 and 45% for chemotherapy alone, 100 and 100% in the R + chemotherapy arm and 95 and 86% for R alone, respectively. Unfortunately, due to the rarity of SMZL, data from clinical trials are sparse, which has hindered development of a standard treatment approach. Current therapeutic options are largely extrapolated from retrospective studies that include outcomes in other types of indolent lymphomas [31].

Nodal MZL

NMZL involves one or more lymph nodes and comprises about 10% of all MZLs and less than 1% of NHL. Typical presentation at diagnosis includes advanced stage nodal disease, with bone marrow involvement seen in less than half of the cases. Median age at diagnosis is 50–62 years, with a slight female predominance (53% of cases) [32]. B symptoms and an elevated LDH are often present, with an elevated serum $\beta 2$ microglobulin seen in about a third of the patients. Cytopenias usually are not present. Thorough workup and staging is necessary to distinguish this entity from the much more common extranodal lymphomas. Like other MZLs, NMZL can be associated with chronic antigenic stimulation related to infections and autoantigens. Like SMZL, the uncommon occurrence of NMZL has limited robust analysis of its risk factors and genetic contributors to etiology.

First-line treatment

As with other indolent lymphomas, initiation of treatment may be deferred in NMZL until disease becomes symptomatic or endangers organ function. Early-stage disease is not common in NMZL, but for patients with localized disease, radiotherapy is the treatment of choice. For patients with advanced stage NMZL, high tumor burden, and symptoms related to disease, treatment guidelines are similar to those used in FL or small lymphocytic lymphoma, with recommendation for R in combination with chemotherapy in eligible patients. Which optimal chemotherapy regimen to combine with R is debatable. Chemotherapy regimens such as cyclophosphamide, vincristine, and prednisone (CVP), CHOP, and fludarabine have been evaluated in this setting. In retrospective studies, CR rates between 30 and 60% were observed when R was combined with alkylator-based therapies like CHOP or CVP [33]. R in combination with purine analog-based therapies such as fludarabine resulted in an ORR of 85%, CR rate of 54%, and 3-year PFS of 79.5% [34]. Bendamustine represents another chemotherapy agent that has been studied alone and in combination with R. It has been shown to be effective in the treatment of many indolent lymphomas, including MZLs. In a retrospective study comparing R-CHOP and R-bendamustine (BR) as first-line treatment for patients with indolent lymphomas, the ORR for BR was 94%, compared with 92% for R-CHOP. CR rates were 63 and 66%, respectively, and BR was found to have a more favorable toxicity profile,

with decreased rates of febrile neutropenia and infection compared with R-CHOP. This study demonstrated that BR is similar in efficacy compared with R-CHOP and should be considered as a first-line treatment option for indolent B-cell NHLs [35].

For patients who cannot tolerate conventional chemotherapy, single-agent alkylators such as chlorambucil with or without R may be used. The immunomodulatory drug lenalidomide has been assessed for efficacy and safety in combination with R in patients with untreated advanced-stage indolent NHLs such as MZL and FL [36]. Of the 27 patients with MZL enrolled on a Phase II trial of this regimen, 18 (67%) achieved a CR, and six (22%) achieved a PR. The ORR for all 110 patients on the trial was 90%, with CR occurring in 63% and PR occurring in 27% of patients [36]. Given the lack of standard therapy in this setting, treatment on a clinical trial should always be considered for patients who are not otherwise candidates for conventional chemotherapy.

Targeting the B-cell receptor pathway with Bruton's tyrosine kinase inhibition in MZL

Increased understanding of the molecular mechanisms underlying other NHLs has opened the door for targeted therapy in MZL. Importantly, most B-cell NHLs express a functional surface B-cell receptor (BCR) that transduces survival signals when active. While constitutive BCR activation is typically associated with somatic mutations in members of the BCR signaling cascade (e.g., CD79a and CARD11 in diffuse large B-cell lymphoma) [37], binding of BCR to a cognate antigen may also activate this survival pathway. This concept is especially important in MZLs, since there is evidence that sustained antigen-mediated BCR activation may play a role in their pathogenesis. As detailed above, MZL is often associated with chronic hepatitis C infection, and some MALT lymphoma sites are associated with other specific infectious pathogens. Several MZL subtypes also show strong associations with certain autoimmune diseases, exemplified by parotid gland MALT lymphoma that may develop in the setting of Sjögren's syndrome. Although data are limited, immunogenetic studies describing biased immunoglobulin gene usage and restricted BCR sequences (termed 'stereotyped' BCRs) in MZLs lend further credence to a role for chronic antigenic stimulation in marginal zone lymphomagenesis and tumor growth and survival [38–40]. Intriguingly, a genetic study of 46 SMZLs identified mutually exclusive somatic mutations in several regulators of NF- κ B, a downstream effector of BCR survival signaling, indicating other possible mechanisms for BCR signal activation in MZLs [41]. Thus, targeting the BCR pathway as a potential driver of MZL pathogenesis (e.g., through inhibition of Bruton's tyrosine kinase [BTK]) represents a rational treatment approach in this lymphoma subtype.

BTK inhibitors in relapsed/refractory MZL

Ibrutinib (Imbruvica; Pharmacyclics, LLC, CA, USA), a first-in-class, irreversible inhibitor of BTK, first demonstrated meaningful clinical utility in chronic lymphocytic leukemia and mantle cell lymphoma [42,43]. This strengthened the evidence supporting a crucial role for BCR activation in B-cell lymphoma survival and further increased interest in this small molecule inhibitor in other subtypes suspected to be heavily dependent on the BCR signaling pathway. The mechanism of ibrutinib is like that of other tyrosine kinase inhibitors: it acts by invading the enzyme's active site and interrupting its ability to propagate signaling, in this case negatively impacting B-cell trafficking, chemotaxis and adhesion. Specifically, ibrutinib forms a covalent bond with a cysteine residue within the active site of BTK. This site has been shown to be crucial for ibrutinib activity, since point mutations at that residue that allow only reversible binding of the drug are associated with ibrutinib resistance [44].

Noy and colleagues set out to evaluate the utility of single-agent ibrutinib in a multicenter, open-label, Phase II trial of patients with relapsed MZL [45]. The primary end point of this study was ORR, with secondary end points including PFS, OS, duration of response, and safety. A total of 63 patients were enrolled, 51% of whom had EMZL; a third of patients had bone marrow involvement. Patients had received a median of two prior lines of systemic therapy (range: 1–9), with 35% of patients having received three or more prior lines of treatment. Seventeen patients received prior monotherapy with R, and 40 patients had undergone R-based chemoimmunotherapy. Enrolled patients received ibrutinib 560 mg by mouth daily for up to 3 years, until disease progression or unacceptable toxicity. Up to two incremental dose reductions were allowed for toxicity (to 420 or 280 mg).

The ORR was found to be 48%, with two patients (3%) achieving CR, by an independent review of the 60 patients with measurable disease at study entry. This was comparable to the investigator-assessed ORR of 53%, with a concordance rate of 84% between the two methods of evaluation. An additional 35% of patients were found to have SD, regardless of source of assessment. When SD was added to the rates of CR and PR, ibrutinib had a clinical benefit rate of 83% by independent assessment. Initial responses occurred at a median of 4.5 months,

and maximal response was found to occur at a median of 5.2 months. At a median follow-up of 19.4 months, median PFS was 14.2 months. Despite similar response rates across MZL subtypes, median PFS was 13.8, 19.4, and 8.3 months for EMZL, SMZL, and NMZL, respectively. Median OS had not been reached at the time of publication, but the authors estimated 18-month OS at 81%.

Safety was evaluated in all 63 enrolled patients, with common treatment-related adverse effects of any grade including fatigue, diarrhea, anemia, nausea, arthralgia, peripheral edema, thrombocytopenia, cough, dyspnea, and upper respiratory tract infection. In the 42 patients who experienced an adverse effect grade 3 or higher, the most commonly reported were anemia (14%), pneumonia (8%), and fatigue (6%). Dose reductions occurred in six patients, with only two of those requiring a second reduction. Discontinuation of therapy for adverse events was rare, but occurred most commonly for diarrhea (3%). Adverse effects of particular interest were bleeding and atrial fibrillation. While the protocol prohibited use of warfarin based on earlier data suggesting increased risk of intracranial hemorrhage with this combination, 29 patients (46%) received another concomitant anticoagulant or antiplatelet agent. Bleeding was reported in 59% of patients, all limited to grade 1 or 2, except for a single incident. That patient developed a grade 5 cerebral hemorrhage 19 days after discontinuation of ibrutinib, and was receiving dalteparin leading up to the bleeding event. The incidence of atrial fibrillation was 6% and in all the cases occurred in patients with other known risk factors. Upon initiation of ibrutinib, seven patients (11%) developed a transient redistribution lymphocytosis, with peak lymphocyte counts occurring at 1 week after ibrutinib initiation and resolution occurring a median of 11 weeks thereafter.

Additional targeted agents being evaluated for their utility in MZL include the PI3K inhibitor idelalisib and the immunomodulator drug (IMiD) lenalidomide. Two isoforms of PI3K are known to be crucial for B-cell development: the ubiquitously expressed PI3K α , and PI3K δ , which is primarily expressed in leukocytes. Activation of either isoform results in generation of PIP3, which helps to recruit key members of the BCR pathway such as BTK, PLC γ 2 and AKT to the plasma membrane. Activation of PLC γ 2 downstream of BTK leads to activation of NF- κ B transcription factors that translocate to the nucleus to promote expression of genes associated with survival and proliferation [46]. Idelalisib (Zydelig; Gilead Sciences, Inc., CA, USA) inhibits PI3K δ , thus limiting proliferation and inducing apoptosis in malignant B cells. In addition to directly inhibiting the BCR pathway, idelalisib inhibits chemokines that controls B-cell trafficking and ultimately reduces the homing and viability of malignant B-cells [47–49]. In a single-arm Phase II study of 125 patients with indolent lymphomas, the ORR for idelalisib at a dose of 150 mg by mouth, twice daily was 56% in all patients and 47% in the 15 patients with MZL [50]. Lymphadenopathy improved in 90% of the entire study population, with 57% of patients having reductions of 50% or more. Nonhematologic adverse effects were most common, including diarrhea, fatigue, and nausea. Grade 3 or higher elevations in transaminases occurred in 13% of patients.

Lenalidomide, on the other hand, does not directly impede the BCR pathway, but exhibits immunomodulatory and antineoplastic activity that has revolutionized therapy for multiple myeloma and has shown activity in both myelodysplastic syndrome and mantle cell lymphoma. In B-cell lymphoma, lenalidomide is thought to act through indirect effects on several types of immune cells in the tumor microenvironment, as well as through direct tumoricidal effects associated with downregulation of the pro-survival factor IRF4 and mediated through lenalidomide's putative target, the E3 ubiquitin ligase cereblon [51]. Given an impressive ORR of 80% with CR rate of 54% in 46 patients with MALT lymphoma, the combination of lenalidomide and R was recently evaluated in the Phase III MAGNIFY trial in multiple indolent lymphomas [52]. Following an induction with daily lenalidomide for 3 of every 4 weeks in combination with R given weekly for four doses, then every 2 months, 15 of the 16 patients with MZL enrolled on this study achieved SD or better, with 63% achieving PR or better (including 25% who experienced CR). Toxicities associated with the combination of lenalidomide and R are primarily hematologic, with grade 3 or 4 neutropenia occurring in 27% of patients, followed by leukopenia in 9% and thrombocytopenia in 6%.

Conclusion & future perspective

MZLs represent a clinical challenge in that their relative rarity, especially of individual subtypes, has largely precluded adoption of a standard management strategy. Treatment options for each MZL subtype in the front-line and relapse setting are summarized in Figure 1. Coupled with the observation that MZLs often develop in the setting of chronic antigen stimulation, insights into the biology underlying pathogenesis in MZL and other indolent lymphomas have highlighted dysregulation of BCR signaling as a potential therapeutic target. Overall, BTK inhibition with ibrutinib illustrates a viable therapeutic approach and validates the role of BTK and the BCR signaling pathway in MZL. The response rates reported by Noy and colleagues appear impressive for a single agent in a population where over half

Figure 1. Treatment considerations in marginal zone lymphoma.
H. pylori: *Helicobacter pylori*; MZL: Marginal zone lymphoma; R: Rituximab.

of the patients had received two or more prior lines of systemic therapy. Importantly, tumor reduction was seen in 78% of patients and objective responses were durable. Furthermore, ibrutinib is a once-daily oral medication that is well tolerated overall, with fatigue, diarrhea, and anemia being the most common treatment-related adverse events. In January 2017, the US FDA approved ibrutinib for the treatment of patients with MZL who have received at least one prior anti-CD20-based therapy and who require systemic therapy. This represents the first approval of an agent specifically for this patient population and has sparked the development of other clinical trials examining novel agents in various indications for patients with MZL. Additional areas of interest for this agent include activity in the front-line setting, rational therapeutic combination regimens, strategies for sequencing of available therapies, and the incidence and clinical impact of ibrutinib resistance. Much more work is needed to address these issues, which could ultimately contribute to development of an optimized therapeutic approach in MZL.

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Executive summary

Autoimmune disease & chronic infections represent significant risk factors for marginal zone lymphoma

- Sjögren's syndrome increases marginal zone lymphoma (MZL) risk by 30-fold and risk of parotid gland extranodal MZL by a factor of 1000. Systemic lupus erythematosus increases MZL risk by 7.5-fold.
- Specific pathogens are associated with extranodal MZLs involving certain anatomical sites: *Helicobacter pylori* with gastric, *Chlamydia psittaci* with ocular adnexal, *Borrelia burgdorferi* with cutaneous, *Campylobacter jejuni* with small intestine and *Mycobacterium* species with bronchus.

No standard of care currently exists for first-line treatment of MZL

- For asymptomatic patients without cytopenias, B symptoms, and/or autoimmune manifestations, close observation without treatment is often a reasonable strategy.
- In some cases, antimicrobial treatment of an associated infection causes regression of the lymphoma and obviates the need for lymphoma-directed therapy.
- Radiation therapy alone can be effective in control of localized MZL and is curative in some instances.
- Rituximab (R) as monotherapy or in combination with chemotherapy is safe and effective for the treatment of limited-stage MZL, and has largely replaced splenectomy as the front-line treatment of choice for splenic MZL.

Targeting the B-cell receptor pathway as a potential driver of pathogenesis is a rational treatment approach in relapsed MZL

- Novel therapeutic agents that target the B-cell receptor (BCR) pathway include ibrutinib, an irreversible inhibitor Bruton's tyrosine kinase (BTK), and idelalisib, a PI3K δ inhibitor.
- In a recent multicenter, Phase II trial involving 63 patients with relapsed MZL, treatment with single-agent ibrutinib resulted in overall response rate of 48%. The most commonly reported adverse effects grade ≥ 3 were anemia (14%), pneumonia (8%), and fatigue (6%).
- The US FDA recently approved ibrutinib for treatment of MZL patients who have received at least one prior anti-CD20-based therapy and who require systemic therapy. This represents the first approval of an agent specifically for this patient population.
- In a Phase II study of 125 patients with indolent lymphomas, the overall response rate for single-agent idelalisib was 56% in all patients and 47% in the 15 patients with MZL. Nonhematologic adverse effects were most common, including diarrhea, fatigue, and nausea, with 13% of patients having grade ≥ 3 transaminase elevations.
- Although it does not impact the BCR pathway directly, lenalidomide in combination with R also emerged as a treatment regimen for relapsed MZL. Fifteen of 16 MZL patients enrolled on the Phase III MAGNIFY study achieved SD or better, with 63% achieving partial response or better. Toxicities associated with this combination are predominantly hematologic.

Conclusion

- The relative rarity of MZLs has largely precluded adoption of a standard management strategy.
- BTK inhibition with ibrutinib illustrates a viable therapeutic approach and validates the role of BTK and the BCR signaling pathway in MZL pathogenesis.
- Opportunities for further investigation of BCR-targeting agents in MZL include activity in the front-line setting, rational therapeutic combination regimens, strategies for sequencing of available therapies, and the incidence and clinical impact of ibrutinib resistance.

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