Current Treatment Options in Marginal Zone Lymphoma

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Overview
This activity is designed to inform physicians about the current treatment options in marginal zone lymphoma (MZL).

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with head and neck cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Explain the challenges and unmet needs in MZL, including treatment strategies for patients with relapsed MZL
- Describe the importance of anti-CD20 antibodies in the treatment strategy in MZL
- Discuss the emerging clinical data surrounding the first FDA-approved drug for MZL

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Introduction

Background

Marginal zone lymphoma (MZL) is an indolent, mature, B-cell neoplasm comprising 3 distinct entities: nodal MZL, splenic MZL, and extranodal MZL of mucosa-associated lymphoid tissue (MALT) type.[1] It has been estimated that MZL accounts for approximately 10% to 17% of all newly diagnosed lymphomas.[2-4] Extranodal MZL is the most prevalent, accounting for roughly 7% of all lymphomas, while nodal and splenic MZL each account for <2%.[2] MZL more often affects older individuals, with the median age at diagnosis ranging between 65 and 70 years.[5]

The diagnosis of MZL can be challenging in cases where limited tissue is accessible. Moreover, MZL may be easily confounded for other lymphoma subtypes with similar presentations, morphology, or immunophenotypes. Careful consideration by a multidisciplinary team is often required.[6-8] When splenic MZL is suspected, evaluation of blood and bone marrow morphology, immunohistochemistry, and flow cytometry is usually sufficient, although rare cases may require splenectomy.[9] The diagnosis of nodal and extranodal MZL is dependent on providing the pathologist with relevant clinical information as well as a sufficient quantity and quality of material to perform required testing.

The underlying pathobiology of MZL is chronic immune stimulation, frequently caused by infection or inflammation. For example, *Helicobacter pylori* infection is associated with about 90% of gastric extranodal MZL, the most common extranodal MZL.[10,11] *Chlamydophila psittaci* has been associated with ocular adnexal extranodal MZL,[12] *Campylobacter jejuni* and *Achromobacter xylosoxidans* have been associated with extranodal MZL of the small intestine,[13-15] and hepatitis C virus appears to increase the risk of developing splenic and nodal MZL.[16-19]

Treatment

When MZL is clearly associated with an underlying infectious or inflammatory condition, treatment of that condition may arrest progression of the disease and in some cases, especially *H. pylori*-related gastric MALT lymphoma, can result in complete regression of the tumor.[6,20,21] In cases of asymptomatic MZL that are unlikely to be improved by antimicrobial or other locally directed therapy, a watch-and-wait approach may be appropriate.[22]

Anti-CD20 Antibodies and Chemotherapy

MZL typically has prominent expression of CD20, providing strong rationale for targeting it therapeutically. Rituximab alone or in combination with chemotherapy is reported to provide high response rates in patients with MZL and has been advocated for those with recurrent MZL.[23,24] Several phase II studies have demonstrated that rituximab monotherapy is well tolerated and provides clinical responses when administered as a frontline treatment of MZL.[23,25] The phase III RESORT trial compared maintenance rituximab with a retreatment dosing strategy in asymptomatic patients with indolent lymphomas and low tumor burden. Patients who responded to an initial course of 4 weekly doses of rituximab were randomized to receive an additional dose of maintenance rituximab every 3 months or retreatment with an additional 4 weekly doses at the time of progression. The primary endpoint was time-to-treatment failure (TTF). The reported overall response rate (ORR) was 52.1% in patients with MZL (n = 71). In contrast to follicular lymphoma, where there was no clear advantage to the maintenance strategy, patients with MZL or small lymphocytic lymphoma who received rituximab at each recurrence had a median TTF of 1.4 years compared with 4.8 years in those receiving rituximab maintenance (P = .012). The median time to cytotoxic chemotherapy was 6.3 years in the retreatment arm and was not reached in the maintenance arm, (P = .0002). The overall survival (OS) did not differ between the 2 arms.[26]

Several clinical trials have looked at rituximab in combination with bendamustine or other chemotherapy drugs. In a retrospective study, the efficacy of bendamustine combined with rituximab was examined in the first-line treatment of elderly patients with splenic MZL. A complete response (CR) was reported in 19 of 23 patients (83%) and 3 patients (13%) achieved a partial response. The combination treatment was well tolerated. Toxicities were mild and mainly hematological with 16 of 23 (70%) patients experiencing neutropenia.[27] In a multicenter, phase II trial, rituximab plus cyclophosphamide, vincristine, and prednisone produced an ORR of 88% (95% CI, 77-98) with 24 CRs (60%) among 42 patients with previously untreated MZL.[24] The median duration of response was 28.3 months. After a median follow-up of 38.2 months, the estimated 3-year progression-free survival (PFS) and OS were 59% and 95%, respectively. . Grade 3 or 4 adverse effects (AEs) were neutropenia and febrile neutropenia. In an open-label, randomized, phase III noninferiority trial, rituximab plus bendamustine was compared with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in the first-line treatment of patients with indolent and mantle-cell lymphomas (MCLs), including patients with MZL. Patients with MZL did not show a significant improvement in PFS with rituximab plus bendamustine (HR, 0.70; 95% CI, 0.34-1.43; P = .3249).[28] Interestingly, all other subgroups in this study (follicular lymphoma, MCL, and Waldenström macroglobulinaemia) demonstrated a significant benefit of rituximab plus bendamustine over rituximab plus CHOP.[28] Further studies will be useful in elucidating the efficacy of rituximab in combination with bendamustine or other chemotherapy drugs in patients with MZL.

Other treatment approaches

Historically, splenectomy has been considered a frontline treatment option for patients with symptomatic splenic MZL, although more recently, it seems to be falling out of favor relative to systemic therapies.[29,30] Locally directed surgery or radiation therapy may be a reasonable option for localized disease in selected cases of extranodal MZL.

Ibrutinib

Ibrutinib is the first FDA-approved therapy for MZL and is indicated for the treatment of patients with MZL who require systemic therapy and have received at least 1 prior anti–CD20-based therapy. Ibrutinib is a first-in-class, oral inhibitor of Bruton tyrosine kinase, a key signaling molecule in

the B-cell receptor signaling pathway. In a phase II study in patients with previously treated MZL of all subtypes, 63 patients received ibrutinib 560 mg daily until progression or unacceptable toxicity.[31] In 60 evaluable patients with a median follow-up of 19.4 months, the ORR was 48% (95% CI, 35-62) and the median PFS was 14.2 months (95% CI, 8.3-not estimable). Grade 3/4 AEs that occurred in >5% of patients included anemia, pneumonia, and fatigue. Serious AEs of any grade occurred in 44% of patients.[31]

Pathways to Personalized Medicine

Personalized medicine approaches remain in the investigational stages of development in MZL. There are several oncogenic mutations of genes involved in signaling pathways that have been associated with MZL, including Notch, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), B-cell receptor, and Toll-like receptor (TLR) signaling.[32-36] In cases of extranodal MZL, the frequency of genetic aberrations is dependent on the primary site of disease.[37] As a greater understanding of the role of signaling pathways in the development of MZL evolves, there will be opportunities for personalizing therapies. It is unclear, however, whether personalized approaches will improve patient outcomes beyond the current treatment paradigm. Clinical trials will be required to determine the roles of signaling pathway inhibition and personalized medicine for patients with MZL.

Peter Martin, MD, MS, associate professor of medicine in the Division of Hematology/Oncology and chief of the Lymphoma Program at Weill Cornell Medicine in New York, offered his insights on current and emerging treatment approaches in patients with MZL.

Moderator: Can you describe some of the unmet needs in the treatment of MZL?

Dr Martin: Fortunately, MZL has some effective therapies available. Principally, rituximab and rituximab plus chemotherapy are active therapies and tend to provide durable responses. That is not to say these treatment options are perfect; there remains room for improvement.

Two areas in MZL where we can do better are the following: First, among patients with mild forms of MZL who might have symptoms or be at risk of developing symptoms, there is a limited number of less-intensive treatment strategies. Rather than give somebody rituximab plus chemotherapy, it would be attractive to use short courses of easily administered agents. For example, someone with localized intestinal MZL may not be particularly symptomatic but is at risk of having worsening symptoms, and it might be attractive to provide occasional therapy to prevent symptoms from emerging. Second, some patients with refractory or relapsed MZL have poor outcomes with current therapeutic approaches and need novel options. For those patients, coming up with therapies that work in ways that are different than chemotherapy might be necessary.

How do treatment strategies differ between MZL subtypes (MALT, nodal MZL, and splenic MZL)?

This question accurately addresses the fact that MZL is a heterogeneous disorder that we classify as nodal MZL, extranodal or MALT lymphomas, and splenic MZL. Even among these lymphomas, there is significant heterogeneity. For example, extranodal MZL might involve the ocular adnexa or the small intestine or the skin or the thyroid gland. The management of a lot of these extranodal lymphomas may depend on the site and extent of disease.

There are a few obvious treatment strategies that make a difference. Certain lymphomas are associated with a clear underlying cause. In general, MZLs arise in the setting of inflammation, and we may be aware of the underlying source of the inflammation. Splenic MZL is frequently associated with hepatitis C; occasionally, nodal MZL can be associated with hepatitis C. Treating the hepatitis C may be sufficient to result in a significant improvement in the lymphoma. Early-stage gastric MZL, in the absence of certain genetic risk factors, has the high probability of responding to *H. pylori* eradication. There are some data that suggest that some ocular adnexal MZL might respond to eradication of *C. psittaci.* There are some circumstances where the management of MZL is dependent on eradication or treatment of the underlying inflammatory condition. Those are probably the minority of all MZLs.

For the remainder of MZLs, the goal of therapy is not only to prevent lymphoma-related symptoms from arising, but also to minimize treatment-related symptoms. The best way to do that often is through observation, and that can be for any MZL subtype. Rituximab and chemotherapy plus rituximab are reasonable options for all subtypes. Some splenic MZLs can be managed surgically, one of the few lymphomas that has surgical management as an option. This is becoming a less attractive option as more effective and better-tolerated systemic therapies become available.

When is a more proactive treatment approach appropriate in an asymptomatic patient? When should the watchful waiting approach be utilized?

All cancers are treated with 3 goals in mind: to cure them when possible, to help patients live longer when possible, and to always to help patients feel better. As long as those are the guiding principles of management of MZL, you cannot really go wrong. Occasionally, localized MZLs can be cured. If patients can be cured in a way that does not induce a lot of toxicity, then that is a reasonable approach. Very often, patients have asymptomatic localized MZL that is in a challenging place to treat, or a systemic MZL, and under these circumstances, the probability of improving somebody's survival by intervening immediately or making them feel better by intervening immediately is very low.

It is important to evaluate whether the lymphoma is likely to cause symptoms in the immediate future. If so, initiating therapy is reasonable. There are official guidelines for clinical trial purposes in follicular lymphoma, called Groupe d'Etude des Lymphomes Folliculaires criteria, which can be applied to MZL, but nothing can replace the combined judgment of a clinician and patient based on repeated interactions and mutual understanding. As we learn more about certain risk factors for lymphomas or risk factors that are involved in the pathogenesis of MZL, that may evolve

over time. For example, if we find that some genetic mutations are likely to be associated with a poor prognosis, that might precipitate earlier therapy. Or, if the lymphoma can be managed by treatment of the underlying condition and not treating the lymphoma, then that is appropriate.

In your opinion, what are some of the promising agents on the horizon that could potentially change the treatment paradigm for MZL?
Increasingly, we are learning more about the biology that drives MZL and the associated heterogeneity. There are clearly roles for multiple signaling pathways, including a B-cell–receptor signaling pathway, a JAK/STAT signaling pathway, TLR signaling, and Notch signaling. There may be a role for antiapoptosis proteins like BCL-2. Provided the interaction between MZL and the microenvironment, immunotherapy might have a role in the future.

Correct identification of active pathways is required through either functional assays or mutational analyses. Clinical trials are required to demonstrate that inhibiting those pathways improves our ability to target the right therapy to the right patient. These are long-term goals in our field. In the short term, the most promising agent on the horizon is probably the agent that was just approved by the FDA for MZL, which is ibrutinib. Ibrutinib provides the opportunity for additional trials in MZL to potentially evaluate which patient population might benefit and evaluate potential combination strategies. Ibrutinib and other B-cell–receptor signaling pathway inhibitors are the most obvious agents to study right now.

The results of the phase II trial, PCYC-1121, were important to the January 2017 FDA approval of ibrutinib in relapsed/refractory MZL. Can you provide us with a brief overview of the findings from this study and the clinical implications?
The study that the FDA approval was based on was called the PCYC-1121 trial. This was an international phase II trial in which 63 patients with previously treated MZL received ibrutinib until time of progression or unacceptable toxicity or withdrawal from therapy for other reasons. These 63 patients had a mix of different kinds of MZL. About half of them had extranodal MZL, and about a quarter each had splenic or nodal MZL. These were typical patients with MZL, with an average age in the mid-60s but ranging from quite young to up to early 90s. Patients had an average of 2 prior therapies. Most commonly, patients had received rituximab plus chemotherapy, and about a quarter of them had received rituximab only. Some patients had received up to 9 prior therapies, so it was a pretty heterogeneous patient population.

In general, the ibrutinib was well tolerated by this patient population. The AEs or toxicity profile were consistent with the toxicity profile seen in other clinical trials in chronic lymphocytic leukemia (CLL), MCL, or follicular lymphoma. Some reported toxicities included gastrointestinal toxicity, myelosuppression with thrombocytopenia, and arthralgias. For the most part, the rates of grade 3 or 4 toxicity were low.

Ibrutinib produced a modest degree of activity in this patient population, with about 50% of patients responding, meaning that about 50% of people had a more than 50% decrease in the diameter of the lymph nodes or extranodal tumors. Among the patients with stable disease, many of them had a mild reduction in the size of their lymph nodes. About 5% to 10% of patients experienced progressive disease as their best response to ibrutinib.

Interestingly, when looking at the population of patients and the potential variables that might influence response or resistance, all different MZL subtypes responded. The extranodal patients responded, as did the splenic and nodal MZL patients; however, the duration of response seemed to be particularly long in the patients with the splenic MZLs compared with the extranodal or nodal MZLs. It is unclear if the duration of response differences were because of underlying disease biology or due to the prior treatment in patients. It did seem as though patients who had fewer prior therapies or rituximab only may have responded a little bit better than the patients who had had chemotherapy in the past. That might be why better responses were seen with the splenic MZL patients who might have been more likely to receive only rituximab in the past.

This is an interesting research question for the future, for sure. Are there differences in these different types of MZLs that might make 1 patient population do better than another patient population? This is something that needs attention in future clinical trials. The average PFS was about 14 months in this study, which is consistent with MCL and not as good as CLL, but a reasonable outcome for a well-tolerated treatment.

Can you discuss promising combination therapies that are being utilized in patients with MZL? How is radioimmunotherapy being utilized?
Radioimmunotherapy is probably something I would be unlikely to include in my treatment regimen for most patients with MZL, unless there is strong rationale for including it. It was included in some of the earlier clinical trials in MZL, and it clearly has activity. However, for whatever reason, clinicians have not widely adopted its use. There are a few scenarios where its use is interesting. For example, in patients with chemotherapy-refractory MZL, it can be an effective option, although radioimmunotherapy may not be as attractive as ibrutinib-based therapy. Radioimmunotherapy demonstrated some activity in ocular adnexal MZL, but the toxicity is not justified by the efficacy in those cases, in my opinion. It is difficult to know where to recommend radioimmunotherapy other than for refractory cases.

Regarding combination therapies, there are not a lot of promising combinations that are currently in the clinic. It is likely we will see combination therapies in the future, in particular with ibrutinib plus rituximab. Considering rituximab is commonly used in MZL treatment, its use in combination with other therapies is a reasonable approach.

What are the toxicity concerns with some of the novel drug agents in the treatment of MZL?
A lot of the newer agents are meant to be used continuously. There are certain toxicities that are associated with chronic use of an agent, where even mild toxicity, drawn out over many months or years, could become a significant nuisance to patients. It is difficult to compare the chronic low-grade toxicity with the more acute and significant toxicity that we run into with immunochemotherapy. Detailed discussions between clinicians

and patients are necessary to determine what each patient values and what their abilities are to tolerate short-term or long-term toxicities of different degrees. There is no question that some of these continuous therapies are going to have some toxicities. In general, these agents are better tolerated than chemotherapy, but are also given over longer periods of time. One of the toxicities that we will all have to struggle with as a population is financial toxicity—that is associated with some of these newer drugs.

How may B-cell receptors, JAK/STAT, NF-κB, Notch, and TLR signaling pathways help evolve personalized treatment approaches?

MZL is a great target for personalized medicine approaches, but it's still in the investigational stages. Currently, there is 1 drug that's approved for MZL, which is ibrutinib. There are no other approved drugs in MZL for all the other noted pathways (eg, JAK/STAT signaling pathway, TLR signaling, and Notch signaling). If we could sequence every single MZL, it is not clear we would necessarily be able to offer the therapies that the sequencing data might suggest we should. Additionally, it remains to be seen whether the personalized medicine approach improves patient outcomes beyond the outcomes already seen with our current approaches. For example, patient outcomes may be decent with observation and single-agent rituximab, regardless of whether a TLR signaling pathway is overactive.

There is room for improvement in MZL disease treatment, and personalized medicine is an attractive approach, as we understand there is a role of these signaling pathways. However, it may be too early to say what role precision medicine will have in the future, and it is too early to start using precision medicine as a standard to manage most patients with MZL.

What is the role of monoclonal antibodies, specifically anti-CD20 antibodies, in the treatment paradigm for MZL?

The anti-CD20 antibodies are some of the most important drugs in the management of most MZLs. They can improve the response to chemotherapy. For example, improvement in response has been demonstrated in extranodal MZL through a phase II trial combining rituximab plus chlorambucil compared with chlorambucil alone.[38] Several clinical trials have looked at rituximab in combination with bendamustine or other chemotherapy drugs, and rituximab is well tolerated and active.[27] Anti-CD20 antibodies clearly have a role whenever chemotherapy is utilized.

In addition, anti-CD20 monoclonal antibodies have significant single-agent activity, and where this has potentially been best studied is splenic MZL. Historically, splenectomy was considered frontline therapy for splenic MZL. Now it is clear that similar results can be achieved using a short course of rituximab alone. Rituximab can sometimes be associated with more AEs than might otherwise be experienced with other indolent lymphomas.

Anti-CD20 antibodies clearly have significant single-agent activity in splenic MZL, and a lot of clinicians are using them in patients with extranodal MZLs or localized extranodal MZLs where chemotherapy or radiation therapy is not appropriate. There is no question that these anti-CD20 antibodies are the mainstay for most patients with MZL and will remain so for the foreseeable future. Unfortunately, these agents do not offer a cure to patients with MZL and can lead to relapse. There is a need to examine new drugs that can work in combination with anti-CD20 antibodies.

What are the challenges when managing the treatment of a patient with relapsed or refractory MZL?

Clinicians need to remember that when managing relapsed MZL, relapse of MZL is not the same as a relapse of diffuse large B-cell lymphoma. If the lymphoma has come back or started to grow, it does not mean that the patient necessarily needs treatment immediately. It is often that patients with progressive MZL can be observed, just as they were observed when originally diagnosed with lymphoma. Clinicians need to be careful not to overtreat people with MZL. On the other hand, there are some patients with MZL who have either a more aggressive variant of MZL, a more chemotherapy-refractory MZL, or can experience transformation to an aggressive histology. Although these patients are the minority, they can be very challenging to manage, and this is where there is clearly an unmet need and new strategies need to be developed.

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