Marginal zone lymphoma - Section 3

From antibiotics to ibrutinib: An array of treatment modalities

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Take Home Messages
- Marginal zone lymphomas represent heterogeneous, indolent, chronic B-cell lymphomas.
- The treatment modalities vary considerably based on subtype and site of involvement. Radiotherapy is the preferred choice for localized stages in EMZL not dependent to microbial pathogens and in patients who failed antibiotic therapy or present local recurrence. Rituximab alone or combined with chemotherapy can be considered in patients with relapsed/refractory localized disease or in disseminated cases. In SMZL, the currently used therapies for symptomatic patients, are rituximab alone with or without maintenance or splenectomy when massive splenomegaly. In NMZL, a similar strategy as that used for FL is proposed.
- Chemotherapy-free approaches have shown some activity but need further investigations.
- A better understanding of the pathogenesis of MALT lymphoma, identifying key molecules in the development or progression of MZLs, may provide the rationale for clinical trials.
- Identification of high risk patients and “risk-adapted” strategies are strongly advisable.

Introduction
Marginal zone lymphomas represent heterogeneous, indolent, chronic B-cell lymphomas. Three subtypes are recognized: the extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT lymphoma), the most common entity of MZL, the splenic marginal zone lymphoma (SMZL) and the nodal marginal zone lymphoma (NMZL). New two novel entities, non-chronic lymphocytic leukemia (non-CLL) monoclonal B-cell lymphocytosis (MBL), probably closely related to SMZL, and a broad category of less well-defined provisional entities primarily involving the spleen, termed splenic B-cell lymphoma/leukemia, unclassifiable (SLLU) have been included in the last WHO classification. The treatment modalities vary considerably based on subtype and site of involvement.

Current state-of-the-art
Extranodal marginal zone lymphoma
EMZL may virtually involve all epithelial tissues and mucosal sites, even those normally devoid of lymphoid tissue. Environment, autoimmune disorders (such as Hashimoto thyroiditis, Sjogren syndrome, Chrohn’s disease) and infectious agents such as Helicobacter Pylori (HP) for gastric MALT lymphoma, Chlamydia Psittaci (CP) for ocular adnexal, Borrelia Burgdorferi (BB) for cutaneous, Campylobacter Jejuni (CJ) for the small bowel, and Achromobacter xylosidans (AX) for the lung, may have a role in the development of EMZLs beside site-specific biologic and genetic abnormalities. Hepatitis C virus (HCV) infection can also have a causative role in the development of MZLs. The management of EMZLs is heterogeneous, including “watch and wait” approach after surgical resection or biopsy, antibiotic therapy, radiotherapy, chemotherapy with or without immunotherapy. In localized H. pylori-positive gastric MALT lymphoma, the initial treatment should be H. pylori eradication. This treatment can induce lymphoma regression and long-term clinical disease control in three-quarter of patients. In H. pylori-negative cases, regression of the lymphoma after antibiotic treatment is less likely and specific anti-lymphoma treatments may be considered. Eradication therapy with antibiotics in MALT lymphoma arising outside the stomach remains investigational. Local therapy includes surgery for localized EMZL at certain sites (breast, thyroid), and radiotherapy that may afford an excellent disease control, particularly in gastric MALT lymphoma using moderate-dose (e.g. 24-30 Gy) involved-field radiotherapy.

Systemic treatment in EMZL is proposed to patients with symptomatic systemic disease, contraindications to radiotherapy, failure after antibiotics or after local therapy (radiotherapy or surgery), and also in those with histologic transformation. Rituximab monotherapy has shown to induce an overall response rate (ORR) of 73%, The IELSG-19 trial is the largest randomized trial which compares chlorambucil alone versus chlorambucil plus Rituximab versus Rituximab alone in EMZL patients. Significantly better 5y-EFS and higher complete response (CR) rates were observed using R plus chlorambucil (CR rates at 78% for Rituximab-chlorambucil vs 65% for chlorambucil alone vs 56% for rituximab alone). PFS and OS did not reach statistical significance. The rituximab-bendamustine combination was
reported with an ORR of 100% (CR rate 75% and 98% after 3 and 6 cycles, respectively). Most patients achieve a complete remission after 4 cycles allowing stopping treatment, thereby avoiding the greater toxicity of longer schedules.\textsuperscript{15,16} Cases with histologic transformation should be treated with chemotherapy and immunotherapy according to the guidelines for DLBCL.

**Splenic marginal zone lymphoma**

In asymptomatic patients an active surveillance (watch and wait) policy is recommended. In patients with concurrent HCV-related chronic hepatitis who do not need immediately conventional treatment of lymphoma, antiviral therapy should be considered.\textsuperscript{17} Several therapeutic options are proposed for symptomatic SMZL. High response rates (ORR 92%, CR rate 44%) are reported with rituximab alone.\textsuperscript{18} Importantly, using a maintenance therapy, many of these responses improve in quality and are long-lasting with a 7-year PFS rate at 75%.\textsuperscript{18} The addition of chemotherapy to rituximab does not further improve the outcome, although this issue is still under investigation. Splenectomy should be recommended only in patients fit for surgery and presenting symptomatic splenomegaly mostly resulting in a rapid improvement of performance status and cytopenia.\textsuperscript{19}

**Nodal marginal zone lymphoma**

For patients with NMZL, a similar strategy as that used for FL is initially proposed.\textsuperscript{20} Patients with strictly localized disease may be considered for localized radiation therapy. In cases of disseminated low tumor burden, a watchful waiting strategy is usually employed, whereas in disseminated high tumor burden, immunochemotherapy such as R-CVP (cyclophosphamide, vincristine, prednisone), FCR (fludarabine, cyclophosphamide, rituximab), 2-CdA +/-R, R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), BR (Bendamustine-rituximab), and R- chlorambucil, is considered appropriate. The most current used is BR that showed a similar median PFS compared to RCHOP (BR, 57.2 months vs R-CHOP, 47.2 months; hazard ratio 0.70, 95% CI 0.34–1.43; p=0.3249).\textsuperscript{21}

**Future perspectives**

In 2017, the US Food and Drug Administration (FDA) approved ibrutinib, a first-in-class Bruton Tyrosine Kinase inhibitor, for the treatment of relapsed/refractory MZL based on pivotal open-label phase II trial demonstrating an overall response rate of 48%.\textsuperscript{22} Other chemotherapy-free regimens have shown activity in MZLs. R- lenalidomide demonstrated high response rate 61% to 92.6% with CR rate of 33% to 70.4% in front line or in the setting of relapsed/refractory EMZL.\textsuperscript{21,22} Bortezomib, demonstrated an ORR of 48%, but with relevant side effects.\textsuperscript{26} Idealisib, was studied in R/R NHLs, including 15 patients affected with MZL (9 EMZL, 5 nodal MZL, 1 splenic MZL): 1 patient with MALT lymphoma showed a CR, while 6 patients showed PR (among the 3 subtypes).\textsuperscript{27} The combination of the new agents with classical therapy is under evaluation. The SELENE study (clinicaltrial.gov identifier: NCT01974440), a phase 3 trial combining Ibrutinib vs placebo in addition to either rituximab plus bendamustine or R-CHOP in previously treated follicular lymphoma and MZL is ongoing. Risk stratification using the specific prognostic indices for EMZL\textsuperscript{28} and SMZL\textsuperscript{29,30} may help the discussion of the new treatment options with patients but these prognostic scores are not validated as tools to decide whether and which treatment is indicated. Nevertheless, more research is needed to identify and validate molecular markers which might lead to better characterize and prognosticate different subtypes of MZL and propose personalized therapies.

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