



Organ-specific considerations for marginal zone lymphomas in Korea, based on Consortium for Improving Survival of Lymphoma (CISL) and Korean clinical studies

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Introduction

The optimal management of marginal zone lymphoma (MZL) has yet to be clearly determined. Antibiotics, surgery, radiation, immunotherapy, and chemotherapy, either alone or in combination, have been previously employed in clinical practice, as well as watchful waiting. It has been well established that localized stage I/II MZL can be properly controlled with local modalities - namely, radiotherapy and/or surgery. A previous retrospective observational study [1] showed 5-year progression-free survival (PFS) and overall survival (OS) rates of 74.7% and 95.9%, respectively. In a later study, the benefit of adding chemotherapy to improve radiotherapy efficacy was not clear [2]. Considering

these findings, local treatment should be considered the principal treatment modality for stage I/II MZL. Considering the indolent natural history of MZL, less toxic chemotherapeutic or immunotherapeutic agents are generally preferred. A prospective rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) clinical trial was conducted as a first-line treatment for advanced stage MZL [3]. There were 24 complete responses (CR) (60%), 11 partial responses (PR) (27.5%), four with stable disease (SD) (10%), and one with progressive disease (PD) (2.5%), yielding a response rate of 87.5% (95% CI, 77.1–97.9%). The estimated three-year PFS and OS were 59.5% and 95.0%, respectively. A more recent retrospective study showed that advanced-stage MZL patients treated with R-CVP had a 3-year PFS rate of 69.6% [4].

Organ-specific treatment considerations for MZL

Gastric MZL (G-MZL)

Treatment of *Helicobacter pylori*-negative G-MZL: According to a retrospective multicenter analysis of 67 *H. pylori*-negative G-MZL patients, 44 patients were treated with *H. pylori* eradication [5]. Among them, 25 patients (56.9%) responded to the initial eradication treatment, including 16 patients with CR (36.4%). Other patients were treated with various local or systemic treatments. After radiotherapy, a CR was achieved in 22 patients (88%). Among 14 patients who received chemotherapy with either cyclophosphamide, anthracycline, vincristine, and prednisone (CHOP) or R-CVP, a CR was achieved in nine patients (64.3%). During the 48.3 months of median follow-up, the G-MZL in one patient transformed into diffuse large B-cell lymphoma (DLBCL) and the patient died. *H. pylori* eradication or radiotherapy could be viable options for treating *H. pylori*-negative G-MZL.

Treatment of *H. pylori* eradication failure in G-MZL: The same study also analyzed a total of 29 *H. pylori*-positive

gastric low grade mucosa-associated lymphoid tissue (MALT) lymphoma patients who received a frontline *H. pylori* eradication regimen consisting of amoxicillin, clarithromycin, and a proton-pump inhibitor [5]. During the follow-up period, 16 patients had refractory G-MZL, nine had probable minimal residual disease, and four relapsed after the eradication regimen. Among the non-responders and relapsed patients, three were subjected to a watch and wait strategy, while 26 underwent second-line treatment including radiotherapy (N=20), chemotherapy (N=5), and chemotherapy plus sequential radiotherapy (N=1). A CR was achieved in all 20 patients (100%) who received radiotherapy. Among the six patients who received chemotherapy (2 CHOP, 2 CVP, 1 R-CVP, and 1 R-CHOP), a CR was achieved in five (83%). No initial clinical response was noted in the remaining patient (17%), however CR was then achieved after undergoing sequential radiotherapy. Probabilities of freedom from treatment failure and OS after 10 years were 83% and 100%, respectively. Radiotherapy appears to be a good option for treating *H. pylori* eradication failure in G-MZL.

Orbital and ocular adnexal MZL (OA-MZL): How to treat localized OA-MZL

Radiotherapy: Localized stage OA-MZL can be controlled fairly effectively via radiotherapy [6]. A previous study demonstrated that localized stage OA-MZL can be controlled quite effectively with low-dose radiation, and its effects can persist for a long duration (more than 5 yr). Even bilateral synchronously involved OA-MZL can achieve 80.9% CR and 16.7% PR with radiotherapy of 27 Gy (range, 20–40 Gy) delivered to each eye [7].

Antibiotics (doxycycline): The use of doxycycline for the eradication of *Chlamydia psittaci* cases of OA-MZL remains controversial. Only one Korean retrospective study has been published thus far [8]. In this trial, 90 patients with histologically confirmed OA-MZL were enrolled. Each patient received one or two cycles of doxycycline (100 mg bid) for 3 weeks. The 5-year PFS rate was 60.9%. Thirty-one patients (34%) showed local treatment failure without systemic spread. Considering the efficacy of doxycycline and the indolent nature of MZL, *C. psittaci*-eradicating antibiotic therapy might prove to be an alternative treatment for elderly patients with OA-MZL or in clinical trial settings.

Chemotherapy: Despite the effective local control of tumor, radiotherapy has the disadvantages of ophthalmologic toxic effects, including late complications such as radiation cataract, xerophthalmia, ischemic retinopathy, glaucoma, and corneal ulceration. In a Korean prospective phase II trial [9], 33 patients with Ann Arbor stage I OA-MZL with the adverse factors were enrolled. They received six cycles of R-CVP followed by two cycles of rituximab therapy. The cumulative CR achievement was 93.9% at 2 years. PFS and OS at 4 years was 90.3% and 100%, respectively. R-CVP could be an alternative frontline therapy for limited-stage

OA-MZL patients with adverse prognostic factors.

Pulmonary MZL (P-MZL): Which is a more optimal treatment modality, surgery or chemotherapy?

The optimal management of P-MZL lymphoma has yet to be clearly determined. Options include watchful waiting, or surgery, chemotherapy, and radiation therapy alone or in combination. Advanced or disseminated P-MZL involving both lungs or extra-pulmonary sites could be controlled via chemotherapy. In the lung, even with localized lesions, radiation and surgical excision of segments or lobes should be carefully considered due to risk of surgical complications, reduction in pulmonary function, and the generally favorable clinical course of MZL itself. In a Korean study that investigated prognosis and optimal approach to P-MZL patients [10], 56 of 61 total patients were treated with surgery (N=22), chemotherapy (12 CVP, 9 R-CVP, 4 CHOP, and 2 R-CHOP) (N=28), or radiotherapy (N=6). Forty-six patients (82.1%) achieved CR or PR. The median PFS was 5.6 years (95% CI, 2.6–8.6). There was no significant difference in PFS between chemotherapy and surgery ($P=0.617$). This finding persisted even in patients with single-lobe or unilateral P-MZL. Thus, in patients for whom surgery is not required for diagnosis, upfront surgery might not be the first-choice P-MZL treatment, in order to preserve lung function and avoid the risks associated with surgery.

Intestinal MZL (I-MZL)

The most frequently observed I-MZL involvement site was the ileo-cecal region (40.7%). Advanced-stage I-MZL cases were observed at a higher rate than in MZL of other sites. Musshoff's stage IE, IIE1, IIE2, IIIE, and IV were present in 44%, 15%, 11%, 7.4%, and 22%, respectively. Considering the clinical features of MZLs, local treatment can be regarded as a principal treatment modality. A high rate of CR was achieved with treatments including local modalities. Even in advanced stages of the disease, surgical treatment was employed in most of the patients (62.5%). This is because almost all patients suffered from subjective symptoms, and the small intestine and ileo-cecal region are difficult regions in which to perform endoscopic biopsy for tissue diagnosis. CR and PR were achieved in 82% and 4% patients, respectively. The estimated 5-year OS and PFS rates were 86% and 54%, respectively. Regardless of stage, I-MZL was controlled relatively well with combined treatment.

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