Gastric marginal zone lymphoma of MALT type: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

E. Zucca1 & M. Dreyling2
On behalf of the ESMO Guidelines Working Group

1Lymphoma Unit, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; 2Department of Medicine III, University Hospital Grosshadern, LMU Munich, Germany

incidence
MALT lymphoma represents about 7% of all non-Hodgkin lymphomas and can arise at any extranodal site; however, at least one third of MALT lymphomas present as a primary gastric lymphoma.

diagnosis
The most common presenting symptoms of gastric MALT lymphoma are non-specific upper gastrointestinal complaints that often lead to an endoscopy usually revealing non-specific gastritis or peptic ulcer with mass lesions being unusual. Diagnosis is based on the histopathologic evaluation of the gastric biopsies [III, A]. The presence of active Helicobacter pylori infection must be determined by histochemistry or, alternatively, urea breath test. In addition to routine histology and immunohistochemistry, FISH analysis or PCR for detection of t(11;18) may be useful for identifying patients that are unlikely to respond to antibiotic therapy [III, B].

staging and risk assessment
The initial staging procedures should include a gastroduodenal endoscopy with multiple biopsies taken from each region of the stomach, duodenum, gastroesophageal junction, and from any abnormal appearing site. Endoscopic ultrasound is recommended to evaluate the regional lymph nodes and the gastric wall infiltration [III, A]. Work-up studies should include complete blood counts, basic biochemical studies, including lactate dehydrogenase and beta 2-microglobulin, computed tomography (CT) scan of the chest, abdomen and pelvis, and a bone marrow aspirate and biopsy [IV, C]. The value of positron emission tomography (PET) scan is controversial and has little clinical utility [IV, D].

treatment plan
Eradication of H. pylori with antibiotics should be employed as the sole initial treatment of localized (i.e. confined to the stomach) H. pylori-positive gastric MALT lymphoma [II, A]. Any of the highly effective anti-helicobacter antibiotic regimens proposed can be used. In case of unsuccessful H. pylori eradication, a second-line therapy should be attempted with alternative triple- or quadruple-therapy regimens of proton-pump inhibitor plus antibiotics. Helicobacter pylori eradication can induce lymphoma regression and long-term clinical disease control in most patients. The length of time necessary to obtain a remission can span from very few months to >12 months. It is reasonable to attend for at least 12 months before starting another treatment in patients who achieve a clinical and endoscopic remission together with eradication of H. pylori, albeit having persistent (residual) lymphoma at the histological level [III, B]. Several studies of post-antibiotic molecular follow-up have shown the persistence of monoclonal B-cells after histological regression of the lymphoma. In these cases, watchful waiting is recommended.

In H. pylori-negative cases or patients who fail antibiotic therapy, irradiation and systemic therapies should be applied depending on the stage of disease; surgery has been not shown to achieve superior results in comparison with more conservative approaches in various trials. Excellent disease control using radiation therapy alone has been reported by several institutions supporting the use of modest dose involved-field radiotherapy (30–40 Gy given in 4 weeks radiation to the stomach and perigastric nodes) for patients with stage I–II MALT lymphoma of the stomach without evidence of H. pylori infection or persistent lymphoma after antibiotic eradication [III, B].

Patients with systemic disease should be considered for systemic chemotherapy [III] and/or immunotherapy with anti CD-20 monoclonal antibodies only if symptoms occur [III]. Only a few compounds and regimens have been tested specifically in MALT lymphomas. Oral alkylating agents (either cyclophosphamide or
chlorambucil) or purine nucleoside analogues (fludarabine, cladribine) can result in a high rate of disease control. The activity of the anti-CD20 monoclonal antibody rituximab has also been shown in phase II studies. Lymphoma with diffuse large cell infiltration should be treated according to the recommendations for diffuse large cell lymphoma.

**response evaluation and follow-up**

Histological evaluation of repeat biopsies remains an essential follow-up procedure. Unfortunately, the interpretation of residual lymphoid infiltrate in post-treatment gastric biopsies can be very difficult and there are no uniform criteria for the definition of histological remission. A strict endoscopic follow-up is recommended, with multiple biopsies taken 2–3 months after treatment to document *H. pylori* eradication and, subsequently, at least twice per year for 2 years to monitor the histological regression of the lymphoma. Gastric MALT lymphomas have limited tendency to distant spreading and to histological transformation. Transient histological local relapses are possible but tend to be self-limiting especially in the absence of *H. pylori* reinfection. In case of persistent but stable residual disease or histological relapses (without distant dissemination and/or gross endoscopic tumour) a watch and wait policy appears to be safe [IV, C], but long term careful endoscopic and systemic follow up (blood counts and minimal adequate radiological or ultrasound examinations) once per year is recommended.

**note**

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading are considered justified standard clinical practice by the experts and the ESMO faculty.

**literature**