EUROPEAN HEMATOLOGY ASSOCIATION

New approaches to indolent lymphoma - Section 3

# *Treatment of extranodal marginal zone B-cell lymphomas (MALT-lymphomas)*

Markus Raderer

*Department of Internal Medicine I, Oncology, Medical University of Vienna, Austria*

## Take-home messages

- Eradication of *Helicobacter pylori* remains the preferred first-line therapy in patients with gastric MALT lymphoma irrespective of stage. Antibiotic therapy can also be given in patients with ocular adnexal MALT-lymphomas as sole initial management.
- The rate of HP-negative gastric MALT-lymphomas, however, is dramatically increasing in large series. Nevertheless, such patients may also be managed with (clarithromycin-based) antibiotic therapy.
- Systemic treatment has increasingly been investigated also in localized disease, and current guidelines have stated curative potential both for systemic therapy as well as local irradiation.
- While promising results have been published for various chemotherapies including cladribine, rituximab plus bendamustine and also chemo-free approaches, no standard therapy has been defined so far. The only randomized data have been generated in a trial comparing rituximab plus chlorambucil versus chlorambucil alone, and a third arm on rituximab alone has been added.

## Introduction

According to the recent WHO classification,[1] extranodal marginal zone B-cell lymphomas of the mucosa associated lymphoid tissue (MALT lymphomas) account for 7- 8% of all newly diagnosed lymphomas. While most prominently encountered in the gastrointestinal tract, MALT lymphoma may arise in virtually any organ of the human body with a different diagnostic, but also therapeutic approach for different localizations. The stomach still remains the most commonly involved organ in patients with MALT lymphoma (amounting for 35-60% of newly diagnosed MALT lymphomas in larger cohorts), followed by the ocular adnexa, lung and salivary glands.

While initially thought to be a localized disease in the majority of patients,[2] more recent data have suggested MALT-lymphoma as a potentially systemic disease from the onset,[3] owing to the homing properties of MALT-lymphoma cells within mucosal structures as well as the potential for late/systemic relapses following local therapy. In view of this, various systemic approaches have been tested in recent years, and guidelines have actually advocated systemic therapies as having equally curative potential in patients with localized disease.[4,5] In addition, the usually highly indolent course of the disease has resulted in increasing attempts to minimize toxicities with application of chemo-free approaches.

## Current therapeutic concepts

One of the most striking properties of MALT lymphoma is the high association of MALT lymphomas with antigenic drives such as bacterial infections and autoimmune diseases. Especially, a high rate of infection with the gram-negative rod *Helicobacter pylori* (HP) reported in up to 90% of gastric MALT lymphomas[1] had been documented, leading to early attempts for HP-eradication as sole management of gastric MALT lymphoma. To date, HP-eradication is still the standard first line treatment for HP-associated gastric MALT-lymphomas irrespective of stage,[4,5] and remissions can be seen in up to 75% of patients. The time to optimal remission, however, may be more than one year in selected cases, so an interval of at least 12 months after documented eradication of HP is necessary to judge the success of antibiotic therapy. Patients who respond to antibiotics alone should not be given further therapy, even in case of histological lymphoma remnants on follow-up biopsies due to the favorable course of such patients.[4-7] A randomized trial had shown no benefit of chemotherapy using chlorambucil over a wait-and-see strategy in patients after HP-eradication,[6] and a retrospective analysis of 107 patients with minimal disease after an interval of one year following antibiotics showed a favorable course in 96% of patients (complete regression with prolonged follow-up in 30% and at least stable disease in 60%), respectively.[7]

## New approaches to indolent lymphoma - Section 3

Of late, some concern has been raised by the increasing rate of patients with HP-negative gastric MALT lymphoma, which has drastically increased to up to 35-50% in larger series. Interestingly, responses to antibiotics have been reported in a relevant percentage of patients with de facto absence of any parameter whatsoever to suggest prior HP infection, including histology, breath-test, stool antigen and serologic testing.[3,8] Thus, antibiotic therapy alone is thought to be a reasonable first line option also in patients with gastric MALT lymphoma without evidence of HP-infection in the relevant guidelines.[4,5] A possible association between *Chlamydophila psittaci* (CP) and ocular adnexal MALT lymphoma (OAML) was detected in an Italian series.[9] While some authors have shown almost 100% CP-positivity in patients with OAML, these findings could not be reproduced in other studies and countries, where CP was totally absent from this cohort of patients. Nevertheless, the use of doxycycline for upfront treatment of OAML has been associated with a rate of CP-eradication of 48%, an overall response rate of 65%, and a 5-year PFS of 55% in patients with stage-I ocular adnexal MALT lymphoma. A retrospective analysis of data from 131 patients receiving doxycycline in OAML has disclosed a CR in 23 (18%), a PR in 36 (27%) and stable disease in 55 (42%) patients, with only 6% progressing.[10] While there was a trend towards better responses in CT-positive patients, doxycycline was rated as a reasonable empirical first-line approach in patients with OAML irrespective of CP-status. For the time being, however, antibiotic therapy remains experimental in other non-gastric MALT lymphomas.

Apart from HP-eradication in gastric MALT lymphoma, no clear recommendations are put forward in the various guidelines following resistance to antibiotics or relapse. In the latter, however, another attempt at eradication may be feasible. Various options exist for treatment of such patients depending on the localization and the clinical presentation.[11,12] In asymptomatic patients, a wait and see strategy might be feasible, as spontaneous 'wax-and-wane' phenomena have been reported especially in OAML and pulmonary MALT lymphomas. In localized disease, excellent results have been reported with radiotherapy with good local control rates, and the 5-year failure-free survival ranges from 60-65% for ocular adnexal MALT lymphoma to 100% for thyroid MALT lymphoma.

More recently, systemic approaches are increasingly being used not only in advanced, but also localized MALT lymphomas due to their potentially curative nature,[4,] and a recent study on 185 patients with extragastric MALT lymphoma followed for a median time of 49 months has also shown no difference in outcome between various therapeutic approaches in localized non-gastric lymphomas in terms of response rates and PFS. Various agents have been used with long-term response rates of up to 100% in some series,[13] but no standard has been defined so far. Interesting options appear application of cladribine, rituximab plus bendamustine or chemo-free approaches including lenalidomide plus rituximab.[14] Only one recent randomized trial (IELSG 19) comparing rituximab plus chlorambucil versus chlorambucil alone[15] showed a response rate of 87% for chlorambucil and 94% for the combination (p=0.069). Complete response rate and 5-year event free survival were significantly higher with the combination (78% versus 65%, p=0.025 and 68% versus 50%, respectively). The IELSG19 study was subsequently amended to add a third arm (rituximab alone). The long term results confirmed superiority of the combination versus either chlorambucil or rituximab monotherapy in terms of event-free and progression-free survival, however, no overall survival benefit was seen.[16]

### References

*1. Isaacson PG, Chott A, Nakumura S, et al. Extranodal marginal cell lymphoma of mucosa-associated tissue (MALT lymphoma). In: Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of the haematopoietic and lymphoid tissues. Lyon, France: IARC 2008:214-9.
*Pathologic basis and background of MALT lymphoma.*
2. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer 1983;52:1410-6.
*3. Raderer M, Kiesewetter B, Ferreri AJM. Clinicopathological characteristics and treatment of marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma). CA Cancer J Clin 2016;66:153-71.
*Concise overview of clinical, molecular and pathological apsects of MALT lymphoma.*
*4. Zucca E, Copie-Bergman C, Ricardi U, et al. Gastric marginal zone lymphoma of MALT-type: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;Suppl 6:vi144-8.
*Consensus statement of the ESMO for application into clinical practice.*
*5. Ruskone-Fourmestraux A, Fischbach W, Aleman B, et al. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. Gut 2011;60:747-58.
*European consensus report involving clinicians, microbiologists and pathologists to discuss various aspects of gastric MALT lymphoma.*
6. Hancock BW, Qian W, Linch D, et al. Chlorambucil versus observation after anti-Helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. Br J Haematol 2009;144:367-75.
*7. Fischbach W, Goebeler ME, Ruskone-Fourmesatrux A, et al. Most patients with minimal histological residuals of gastric MALT lymphoma after successful eradication of Helicobacter Pylori can be managed safely by a watch and wait strategy: experience from a large international series. Gut 2007;56:1685-7.
*Large analysis of gastric MALT lymphomas without further therapy after HP-eradication; important information of management of patients in clinical practice!*

## New approaches to indolent lymphoma - Section 3

8. Raderer M, Wöhrer S, Kiesewetter B, et al. Antibiotic treatment as sole management of Helicobacter pylori-negative gastric MALT lymphoma: a single center experience with prolonged follow-up. Ann Hematol 2015;94:969-73.
9. Ferreri AJ, Dolcetti R, Magnino S, Doglioni C, Ponzoni M. Chlamydial infection: the link with ocular adnexal lymphomas. Nat Rev Clin Oncol 2009;6:658-69.
10. Kiesewetter B, Raderer M. Antibiotic therapy in nongastrointestinal MALT lymphoma: a review of the literature. Blood 2013;122:1350-7.
11. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. Blood 2016;127:2082-92.
12. Desai A, Joag MG, Lekakis L et al. Long-term course of patients with primary ocular adnexal MALT lymphoma: a large single-institution cohort study Blood 2017;129:324-32.
13. Kiesewetter B, Ferreri AJ, Raderer M. Chemoimmunotherapy for mucosa-associated lymphoid tissue-type lymphoma: a review of the literature. Oncologist 2015;20:915-25.
14. Kiesewetter B, Willenbacher E, Willenbaher W, et al. A phase 2 study of rituximab plus lenalidomide for mucosa-associated lymphoid tissue lymphoma. Blood 2017;129:383-5.
15. Zucca E, Conconi A, Laszlo D, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomized study. J Clin Oncol 2013;31:565-72.
16. Zucca E, Conconi A, Martinelli G, Bouabdallah R, et al. Final results of the IELSG-19 randomized trial of mucosa-associated lymphoid tissue lymphoma: Improved event-free and progression-free survival with rituximab plus chlorambucil versus either chlorambucil or rituximab monotherapy. J Clin Oncol 2017; doi: 10.1200/JCO.2016.70.6994 [Epub ahead of print].