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Second Cancers and Residual Disease in Patients Treated for Gastric Mucosa-Associated Lymphoid Tissue Lymphoma by *Helicobacter pylori* Eradication and Followed for 10 Years

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this CME exercise, successful learners will be able to describe the diagnostic criteria, explain the role of *H pylori* eradication in localized gastric Malt lymphoma, and review follow-up strategies after eradication of the bacterium and remission of the lymphoma.

See Covering the Cover synopsis on page 875.

BACKGROUND & AIMS: Cure of *Helicobacter pylori* infection induces remission in most patients with gastric mucosa-associated lymphoid tissue lymphoma (GML) that is associated with these bacteria. We determined the long-term outcomes of these patients in a prospective multicenter trial and investigated whether they developed second cancers or had histologic residual disease. **METHODS:** We followed 120 patients with stage EI1 GML for a median of 122 months after *H pylori* eradication (range, 1–171 months). Remission was determined by histology analysis and development of second cancers was documented. **RESULTS:** Of the patients, 80% (96 of 120) achieved complete remission from GML, and 80% of those (77 of 96) remained disease free. Estimated mean survival time in the Kaplan–Meier analysis was 147 months (95% confidence interval: 138–156 months). Of the patients that achieved complete remission, 17% (16 of 96) had histologic residual disease after a median of 32 months (range, 3–68 months). Disease did not progress in any of these patients, and all but 1 achieved a second complete remission (median duration, 46 months). Standardized morbidity ratios revealed a significantly higher incidence of gastric cancer (8.567; 95% confidence interval, 3.566–20.582) or non-Hodgkin lymphoma (18.621; 95% confidence interval: 8.365–41.448) in the 96 patients that achieved a complete remission, compared with the general German population. **CONCLUSIONS: Cure of *H pylori* infection leads to continuous complete remission in most patients with *H pylori*–associated GML. Patients are at risk for development of secondary cancers (ie, gastric cancer and non-Hodgkin lymphoma).**

Keywords: MALT; Stomach Cancer; Cancer Recurrence; Management Strategy.

Development of gastric mucosa-associated lymphoid tissue (MALT) and gastric MALT lymphoma (GML) is closely linked to *Helicobacter pylori* infection. *H pylori* eradication induces lasting remission of GML in most cases with localized disease. Eradication of the bacterium has been established as the first-choice treatment option for *H pylori*–positive, early-stage GML.[1–8] Molecular follow-up by polymerase chain reaction (PCR) for the rearranged immunoglobulin heavy chain variable region was performed by us and others. The persistence of monoclonal bands is observed in cases showing apparent complete histologic remission (CR), but this has no clinical consequences, despite watchful waiting.[2,3,5,9]

There are 2 major clinical questions regarding eradication therapy in CR patients. First, what is the preferred management of patients with histologic residual disease? Notably, histologic residual disease is also called minimal residual disease and responding residual disease in the literature.[6,10] A watch-and-wait approach has been suggested for these patients.[3,4,6] Second, are MALT lymphoma patients at a higher risk for second cancer, especially gastric cancer?[11–13]

As *H pylori* eradication was the sole treatment in our patient cohort, antecedent toxic therapy, such as radiation or chemotherapy, played no pathogenetic role in the development of second cancer.[14] We enrolled 120 patients with stage EI1 GML in a prospective multicenter trial of sole *H pylori* eradication therapy. Here we present the final analysis after a median follow-up of more than 10 years. This analysis focuses on data concerning remission duration, histologic residual disease, and second cancer, especially second gastric cancer and second lymphoma.

Abbreviations used in this paper: CI, confidence interval; CR, complete remission; GML, gastric mucosa-associated lymphoid tissue lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NHL, non-Hodgkin lymphoma; PCR, polymerase chain reaction.

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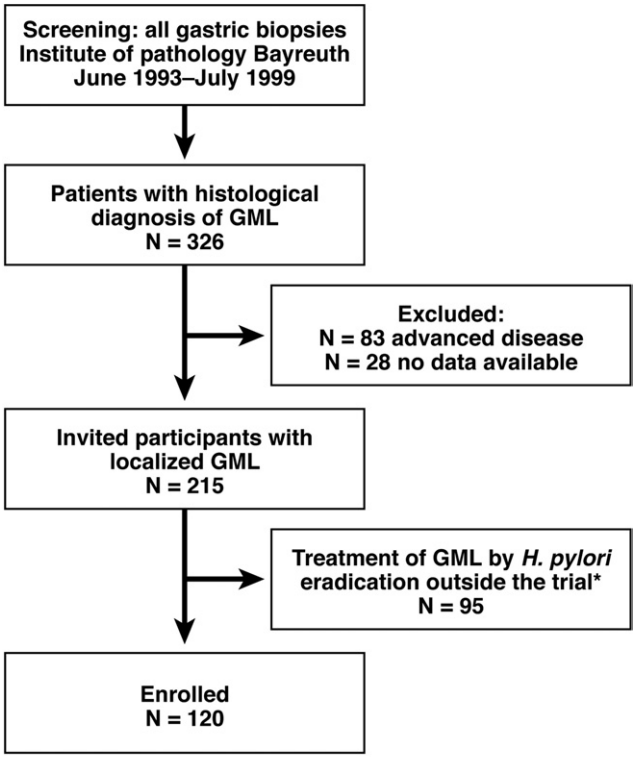

Figure 1. Recruitment of study population.

Methods

Patients

The study population has been described previously.[1–3] This prospective, multicenter trial included 120 patients (63 female, 57 male) with a mean age of 62 (range, 29–88) years, 117 patients were of German, 1 patient of Italian, 1 patient of Portuguese, and 1 patient of West African ethnic background. All patients with positive stage EI1 GML according to the Ann Arbor system, as modified by Musshoff and Radaszkiewicz, where lymphoma is limited to the mucosa and submucosa of the stomach with no lymph node involvement, were eligible for this study.[15] Staging procedures included a clinical examination, full blood count, biochemistry, abdominal ultrasound, imaging of chest and abdomen by computed tomography scan, and endoscopic ultrasound.

Recruitment was from June 1993 until July 1999 as follows: whenever a gastric biopsy specimen referred to our central pathologist (M. Stolte) revealed a gastric MALT lymphoma, the referring physician was informed about the study protocol and asked to enroll the patient. If staging revealed stage EI1 disease and patients gave their written informed consent, they were included in the study.

In the years 1993 to 1999, three hundred twenty-six GMLs were diagnosed histologically at the Institute for Pathology Bayreuth, of which 120 patients were enrolled in this trial (Figure 1). Ninety-six patients came from physicians and gastroenterologists in private practice and 24 from medical centers from all over Germany. In a retrospective analysis of the remaining 206 patients, 83 were reported to have more advanced disease and were referred to alternative initial treatment or a watch-and-wait policy as applied in indolent lymphoma, excluding them from this study. No information could be obtained from 28 patients, as repeated sent questionnaires were incomplete or not returned. Finally, 95 patients were treated outside the trial by sole *H pylori* eradication. These patients were lost due to lack of referral or lack of consent. They also often had incomplete lymphoma staging and irregular endoscopic follow-up. Results for these patients were published among a retrospective series of 196 patients treated outside a clinical trial by sole *H pylori* eradication with a standard regimen.[16]

Treatment of study patients involved a 2-week course of amoxicillin (3 × 750 mg daily) and omeprazole (3 × 40 mg daily). Second-line treatment consisted of a triple regimen containing omeprazole (2 × 20 mg daily), metronidazole (3 × 400 mg daily), and clarithromycin (2 × 250 mg daily) for 10 days.

Initially, endoscopic controls were carried out at monthly intervals. After CR, endoscopic controls were continued every 6 to 12 months. Clinical follow-up without endoscopy was performed when the patient refused further endoscopies or the treating physician decided against endoscopy due to comorbidities. Second cancers were documented during follow-up. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice requirements. The protocol was approved by the local ethics committees of the University Erlangen-Nuremberg and Humboldt-University, Berlin. All patients gave written informed consent.

Pathologic and Molecular Analysis

Histologic analysis was the standard for assessing remission status. Presence of *H pylori* was demonstrated by Warthin-Starry staining. Diagnostic criteria for GML were unequivocal evidence of lymphoepithelial destruction and replacement of gastric glands by uniform centrocyte-like cells.

All biopsies were graded according to the Updated Sydney System.[17] In addition, presence of lymphoepithelial lesions, stromal changes (ie, empty tunica propria, fibrosis, atrophy), and lymphoid infiltrate (ie, aggregates and follicles) were evaluated.

Lymphoid infiltrate in post-treatment biopsies revealing monotonous infiltrates of centrocyte-like cells and/or lymphoepithelial lesions was considered histologic residual lymphoma. Histologic residual lymphoma is referred to as histologic residual disease. DNA isolation for monoclonality studies, RNA isolation from frozen and paraffin-embedded gastric biopsies for translocation t(11;18), and sequencing analysis of GML and second diffuse large B-cell lymphoma were performed as described previously.[2,18] All molecular data were collected without reference to the clinical and histologic data.

Remission Evaluation

CR was diagnosed as macroscopic disappearance of lymphoma and absence of histopathologic evidence of lymphoma on biopsy in 2 consecutive investigations. Partial remission was diagnosed macroscopically as at least a 50% tumor reduction and histologically by the presence of both signs of regression (eg, empty tunica propria and lower density of atypical lymphoid infiltrates) and lymphoma (focal lymphoepithelial lesions). No change was diagnosed when no macroscopic or histologic changes were present.

Cases with no change and partial remission were referred for alternative treatment. Cases diagnosed as CR were followed up further and scored as continuous CR when normalization of macroscopic findings continued and all follow-up biopsies con-