GASTRIC CANCER

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

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Background: Eradication of *Helicobacter pylori* is the established initial treatment of stage I MALT (mucosa associated lymphoid tissue) lymphoma. Patients with minimal persisting lymphoma infiltrates after successful eradication of *H pylori* are considered treatment failures and referred for radiation, chemotherapy, immunotherapy, or surgery.
Aim: To report a watch and wait strategy in such patients.
Methods: 108 patients were selected from a larger series of patients treated at various European institutions. Their mean age was 51.6 years (25 to 82), and they were all diagnosed as having gastric marginal zone B cell lymphoma of MALT type stage I. After successful *H pylori* eradication and normalisation of the endoscopic findings, lymphoma infiltrates were still present histologically at 12 months (minimal histological residuals). No oncological treatment was given but the patients had regular follow up with endoscopies and multiple biopsies.
Findings: Based on a follow up of 42.2 months (2–144), 102 patients (94%) had a favourable disease course. Of these, 35 (32%) went into complete remission. In 67 (62%) the minimal histological residuals remained stable and no changes became evident. Local lymphoma progression was seen in four patients (5%), and one patient developed a high grade lymphoma.
Conclusions: Most patients with minimal histological residuals of gastric MALT lymphoma after successful eradication of *H pylori* had a favourable disease course without oncological treatment. A watch and wait strategy with regular endoscopies and biopsies appears to be safe and may become the approach of choice in this situation. Longer follow up is needed to establish this definitively.

A decisive role in the development and progression of gastric MALT (mucosa associated lymphoid tissue) lymphoma is played by *Helicobacter pylori* (*H pylori*). Twelve years ago, *H pylori* eradication was introduced into the treatment of this specific lymphoma.[1] Since then, several studies have confirmed its efficacy, leading to complete remission of the lymphoma in some 80% of cases.[2–6] Nowadays, eradication of the bacterium is the accepted initial treatment of choice worldwide in stage I gastric MALT lymphoma. Recent follow up reports have impressively demonstrated that *H pylori* eradication also provides a favourable long term outcome, with a genuine chance of cure or at least of long lasting complete remission in the majority of patients.[7 8]

Patients not responding to eradication therapy and those with a negative *H pylori* status are usually referred for radiation or sometimes for surgery, chemotherapy, or immunotherapy, or combinations of these. Up to now, the same established options are offered to patients with persistent residual lymphoma infiltrates on histology (''minimal residual disease'') despite successful *H pylori* eradication and normalisation of the endoscopic findings. Such patients are classified as treatment failures following *H pylori* eradication. However, in a small series we have recently shown that patients with minimal residual disease can also have a favourable prognosis.[9] For them, oncological therapy probably represents overtreatment.

In this report of a large clinical retrospective case series, we show that a watch and wait strategy with regular endoscopies and biopsies is a justified approach in patients with minimal residual disease.

METHODS

We recruited 108 patients—62 male, 46 female, mean age 51.6 years (range 25 to 82)—with newly diagnosed gastric marginal zone B cell MALT lymphoma from the European gastrointestinal lymphoma study (EGILS) group in Germany, France, Italy, and Austria, and analysed the outcome in retrospect. *H pylori* infection was demonstrated histologically or by the rapid urease test. Complete diagnostic work up, including endoscopic ultrasound, revealed stage I MALT lymphoma in all cases according to the Ann Arbor staging system. Endoscopic ultrasound was not, however, undertaken in every case. All patients became *H pylori* negative after one or more courses of eradication therapy.

Twelve months after successful *H pylori* eradication, patients were classified as having minimal histological residuals if they met the following criteria: disappearance of any endoscopic lesion with the exception of harmless features of post-*H pylori* gastritis and the presence of a lymphoid infiltrate in post-treatment biopsies, revealing monotonous infiltrates of centrocyte-like cells or lymphoepithelial lesions, or both (corresponding to the findings that have also been described as histological residual disease[8] or responding residual disease according to Copie-Bergmann[10]).

Abbreviations: EGILS, European gastrointestinal lymphoma study; GELA, Groupe d'Etude des Lymphomes de l'Adulte; MALT, mucosa associated lymphoid tissue

Any further treatment was postponed on the understanding that there would be very thorough clinical and endoscopy/biopsy follow up. Follow up investigations with obligatory endoscopies and biopsies, carried out every three to six months in the first two years, with extension to six monthly and yearly intervals thereafter. In this follow up period, patients were categorised into complete remission (normal endoscopic and histological findings on three consecutive occasions), minimal histological residuals according to the criteria described above, and progressive disease if there was endoscopic or histological progression of the lymphoma or high grade transformation.

RESULTS

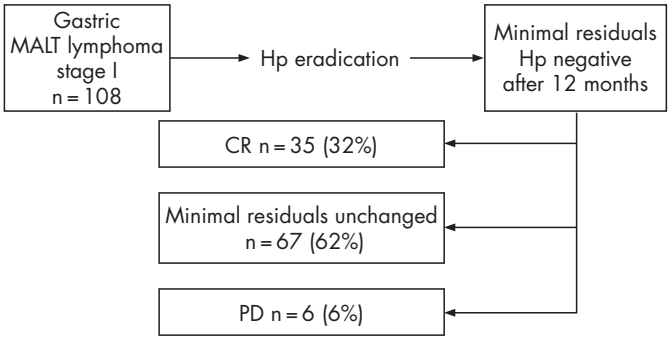
Median length of follow up was 42.2 months (range 2 to 144), starting one year after successful eradication of *H pylori*. Follow up was 35.9 and 57.5 months for patients achieving minimal histological residual disease and complete remission, respectively. Figure 1 summarises the outcome in all 108 patients. Thirty five patients (32%) were found to enter into late (>12 months after *H pylori* eradication) and continuous complete remission, while 67 (62%) showed stable minimal histological residuals, as outlined above, and did not have any signs of local or systemic progression or high grade transformation. The disease course was therefore favourable in 94% of all patients. The results were quite similar when focusing only on those patients with a follow up of more than 24 months: complete remission in 30/80 (37.5%), minimal histological residuals in 44/80 (55%), and progressive disease in 6/80 (7.5%).

Local lymphoma progression diagnosed by endoscopy and histology was seen in five patients (5%) after 18, 24, 35, 60, 74 months, respectively. In one patient lymphoma recurrence was accompanied by *H pylori* reinfection. Complete remission of the lymphoma was achieved for an observation period of 18 months after successful treatment of the reinfection. One patient (1%) developed high grade gastric lymphoma and was treated with chemotherapy. Two patients with minimal residual disease died from secondary malignancies (colon carcinoma and urothelioma).

Detailed findings on the depth of gastric wall infiltration by endoscopic ultrasound at the time of initial diagnosis are only available in a subset of patients. The majority of patients (33 of 37) were in endosonographic stage I1 (infiltration of mucosa or submucosa). Of the four patients with infiltration of the muscularis propria or serosa, one developed progressive disease while the other three revealed unchanged minimal histological residuals.

DISCUSSION

The convincing evidence for a pathogenic role of *H pylori* in gastric MALT lymphomas—as shown by epidemiological data, morphological and molecular-biological studies, and animal experiments—inevitably involved considerable therapeutic effort. In 1993, Wotherspoon *et al* reported complete regression of gastric MALT lymphoma following successful eradication of *H pylori* in five of six cases.[1] Since then, several prospective trials have confirmed this observation, suggesting an overall success rate of about 80% in stage I disease.[2–6] However, this fascinating therapeutic option was under debate until very recently. There was some doubt as to whether the high rates of lymphoma regression in fact represent long term treatment success. In the meantime, long term follow up studies have become available that impressively demonstrate that this is indeed the case and suggest that *H pylori* eradication provides a genuine chance of cure in the majority of these patients.[7 8]



Hp: helicobacter pylori; CR: complete remission; PD: progressive disease

Figure 1 Outcome of patients with minimal histological residuals of gastric MALT lymphoma after successful eradication of *H pylori*.

It is well accepted that patients who do not respond to *H pylori* eradication therapy or who are definitely negative for *H pylori*, as demonstrated serologically, as well as those patients who suffer from disseminated lymphoma (stage II to IV) should be referred for oncological treatment or combination therapy. For decades, surgical resection was the preferred treatment of gastric lymphoma. In a large prospective study we have shown that surgical resection followed by radiation, depending on lymphoma stage and residual tumour status, is a convincing concept in gastric MALT lymphoma in stages I and II.[5] In recent years, there has been increasing evidence that exclusive radiotherapy offers comparable therapeutic efficacy.[11 12] Against the background of a better quality of life, a conservative approach using radiation or chemotherapy is nowadays considered as the treatment of choice in stage I and II gastric MALT lymphoma if *H pylori* eradication therapy fails. However, oncological treatment is also associated with potential acute toxicity and late complications.

In view this, the data presented here offer real benefit for patients with minimal histological residual disease after eradication of *H pylori*. The vast majority of our patients had a favourable outcome. We do not know the strain of *H pylori* or the translocation t(11;18) status, which were beyond the scope of this clinical series.[13 14] Our motivation for this study was to summarise our experience of patients with gastric MALT lymphoma who had chosen, for individual reasons, to accept a watch and wait strategy in the case of minimal histological residual disease, after eradication of *H pylori*. The difficulties of collecting sufficient numbers of cases have to be kept in mind.

Of patients with minimal histological residuals following *H pylori* eradication, many obviously enter into late (>12 months after successful *H pylori* eradication) complete remission of the lymphoma. Some showed complete regression for up to 24 months after elimination of the bacterium. Owing to variations in the numbers and intervals of endoscopic examinations and in the documentation of the cases we cannot clearly state the exact lapse time. However, a threshold of 12 months, as adopted by an unwritten consensus, seems questionable. Though sampling error may have contributed to a false diagnosis of definite complete remission in some cases, the period of observation required for a definition of treatment failure after *H pylori* eradication should be extended beyond 12 months.

As one third of our patients achieved complete remission and almost two thirds had unchanged minimal histological residuals, oncological treatment—such as radiation, surgery, or chemo-/immunotherapy—may represent overtreatment in the individual case. It has to be emphasised, however, that strict criteria of minimal histological residuals must be met. We included only those patients with histological features that have been accepted in published reports as histological residual disease or responding residual disease.[8 9 10] All national reference pathologists engaged in this clinical series were in

agreement with these criteria. However, there was no specific predefined classification system. In view of possible bias by sampling error with biopsies and difficulties in histological interpretation, the EGILS group also emphasises the need to include normal endoscopic findings as a criterion for minimal histological residuals, as done here. Future studies need to show whether a strictly defined description of minimal residuals, as outlined in the recent GELA classification,[10] a very thorough description of the lymphoma infiltration of the different layers of the gastric wall by endoscopic ultrasound,[15] or molecular genetic findings such as the translocation t(11;18) will serve as still better predictors of the course of disease. There is also a need for careful long term follow up, as we cannot exclude late relapses, as seen after conventional therapy in a substantial proportion of cases.[16]

Conclusions

We believe that a watch and wait strategy involving close follow up with regular endoscopies and biopsies is a valid new approach in patients with clear cut minimal histological residuals of gastric MALT lymphoma, after successful eradication of *H pylori*.

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REFERENCES

1 **Wotherspoon AC**, Doglioni C, Diss TC, *et al*. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet* 1993;**342**:575–7.
2 **Bayerdörffer E**, Neubauer A, Rudolph B, *et al*. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of Helicobacter pylori infection. *Lancet* 1995;**345**:1591–4.
3 **Roggero E**, Zucca E, Pinotti G, *et al*. Eradication of Helicobacter pylori infection in primary low-grade gastric lymphoma of mucosa-associated lymphoid tissue. *Ann Intern Med* 1995;**122**:767–9.
4 **Ruskone-Fourmestraux A**, Lavergne A, Aegerter PH, *et al*. Predictive factors for regression of gastric MALT lymphoma after anti-Helicobacter pylori treatment. *Gut* 2001;**48**:297–303.
5 **Fischbach W**, Dragosics B, Kolve-Goebeler ME, *et al*. Primary gastric B-cell lymphoma: results of a prospective multicenter study. *Gastroenterology* 2000;**119**:1191–202.
6 **Neubauer A**, Thiede Ch, Morgner A, et al. Cure of Helicobacter pylori infection and duration of remission of low-grade gastric mucosa-associated lymphoid tissue lymphoma. *J Natl Cancer Inst* 1997;**89**:1350–5.
7 **Fischbach W**, Goebeler-Kolve M-E, Dragosics B, *et al*. Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive Helicobacter pylori eradication therapy: experience from a large prospective series. *Gut* 2004;**53**:34–7.
8 **Wundisch T**, Thiede C, Morgner A, *et al*. Long-term follow-up of gastric MALT lymphoma after Helicobacter pylori eradication. *J Clin Oncol* 2005;**23**:8018–24.
9 **Fischbach W**, Goebeler-Kolve M-E, Starostik P, *et al*. Minimal residual low-grade gastric MALT-type lymphoma after eradication of Helicobacter pylori. *Lancet* 2002;**360**:547–8.
10 **Copie-Bergman C**, Gaulard P, Lavergne-Slove A, *et al*. Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma. *Gut* 2003;**52**:1656.
11 **Koch P**, Probst A, Berdel WE, *et al*. Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96). *J Clin Oncol* 2005;**23**:7050–9.
12 **Tsang RW**, Gospodarowicz MK, Pintilie M. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol* 2003;**21**:4157–64.
13 **Liu H**, Ye H, Ruskone-Fourmestraux A, *et al*. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. *Gastroenterology* 2002;**122**:1286–94.
14 **Montalban C**, Santon A, Redondo C, *et al*. Long-term persistence of molecular disease after histological remission in low-grade gastric MALT lymphoma treated with H. pylori eradication. Lack of association with translocation t(11;18): a 10-year updated follow-up of a prospective study. *Ann Oncol* 2005;**16**:1539–44.
15 **Fischbach W**, Goebeler-Kolve M, Greiner A. Diagnostic accuracy of EUS in the local staging of primary gastric lymphoma: results of a prospective, multicenter study comparing EUS with histopathologic stage. *Gastrointest Endosc* 2002;**56**:696–700.
16 **Raderer M**, Streubel B, Woehrer S, *et al*. High relapse rate in patients with MALT lymphoma warrants lifelong follow-up. *Clin Cancer Res* 2005;**11**:1–4.