VOLUME 23 · NUMBER 31 · NOVEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Follow-Up of Gastric MALT Lymphoma After *Helicobacter Pylori* Eradication

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Submitted April 18, 2005; accepted July 25, 2005.

Supported by the Deutsche Krebshilfe (grant 70 2251), the Gesellschaft für Gastroenterologie in Bayern, Germany, and the Leukemia Research Fund, UK.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2331-8018/$20.00

DOI: 10.1200/JCO.2005.02.3903

ABSTRACT

Purpose
Cure of infection induces remissions in most patients with early stage *Helicobacter pylori* (*Hp*) positive gastric MALT (mucosa-associated lymphoid tissue) lymphoma (GML). We tracked the long-term stability of remissions in this prospective, multicenter trial.

Patients and Methods
In 120 patients with stage I_{1E} disease, we performed sequential endoscopic-bioptic follow-up after *Hp* eradication and polymerase chain reaction of the rearranged immunoglobulin heavy chain gene. The status of t(11;18) was assessed in 65 patients.

Results
Median follow-up was 75 months (range, one to 116). Five-year survival was 90%. Eighty percent of patients (96 of 120) achieved complete histologic remission (CR). Eighty percent of CRs are in continuous complete histologic remission (CCR). Three percent of CR patients (three of 96) relapsed and were referred for alternative treatment. Seventeen percent of CR patients (16 of 96) showed histologic residual disease (RD) during follow-up; a watch-and-wait strategy was applied, and all entered into a second CR. After a median follow-up of 63 months, 14 of 52 analyzed patients reaching CR showed ongoing B-cell monoclonality. Fifteen percent of GMLs were t(11;18) positive. Both t(11;18) and ongoing monoclonality were associated with a significantly higher risk for no response or relapse ($P = .004$, $P = .007$), but also present in patients in CCR. Early gastric cancer was diagnosed in three cases during follow-up.

Conclusion
Cure of *Hp* infection results in CCR in most patients. Histologic RD, B-cell monoclonality, and t(11;18) were present in a considerable number of CR patients. A watch-and-wait strategy is justified when close follow-up is guaranteed.

J Clin Oncol 23:8018-8024. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Development of gastric MALT (mucosa associated lymphoid tissue) and gastric MALT lymphoma (GML) is closely linked to *Helicobacter pylori* (*Hp*) infection.[1-5] Several studies indicate that *Hp* eradication induces regression of GML in most cases.[6-11] Because of its obvious advantages over alternative treatment strategies, eradication is currently widely used as the first-choice treatment option for *Hp*-positive, early-stage GML. Radiotherapy is an established salvage treatment.[12]

B-cell monoclonality is a common finding at diagnosis and in follow-up biopsies with the lymphoma in complete histologic remission (CR).[9,10,13] Interpretation of a monoclonal (MC) polymerase chain reaction (PCR) is difficult; so far, there are no conclusive data available regarding whether patients with ongoing monoclonality experience a somewhat

higher relapse rate. In addition, monoclonality is frequently found in simple gastritis cases with lymphoid follicles and reportedly, precedes lymphoma development.[14-17] The recurrent translocation t(11;18, q21;q21) is found in 24% to 48% of GMLs, often as the only aberration.[18-20] Progression with transformation into high-grade lymphoma is reported to be unlikely in t(11;18)-positive lymphomas.[21] Positive cases are described as not responding to *Hp* eradication.

We enrolled 120 patients with stage I_{1E} GML in a prospective multicenter trial of sole *Hp* eradication therapy. We focus here on data concerning remission duration, B-cell monoclonality, histologic residual disease (RD), relapse, and possible therapeutic consequences. Additionally, we assessed the translocation t(11;18) at diagnosis in 65 patients in retrospect and present data on second early gastric cancers.

PATIENTS AND METHODS

Patients

This prospective, multicenter trial included 120 patients (63 female, 57 male) with a mean age of 62 years (range, 29 to 88 years) with *Hp*-positive stage I_{1E} GML, according to the Ann Arbor system as modified by Musshoff, where lymphoma is limited to the mucosa and submucosa of the stomach with no lymph node involvement.[22] Staging procedures included full blood count, biochemistry, abdominal ultrasound, imaging of chest and abdomen by computed tomography scan, and endoscopic ultrasound. Treatment 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 achievement of histologic CR, endoscopic controls were continued every 6 to 12 months. Patients having no change (NC) after 2 months or partial remission (PR) after 6 months were regarded as treatment failure. 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 ethical committees of the University Erlangen-Nuremberg and Humboldt-University, Berlin. All patients gave written informed consent.

Pathologic Analysis

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

All biopsies were graded according to the Updated Sydney System.[23] In addition, presence of lymphoepithelial lesions (LELs), stromal changes (ie, empty tunica propria, fibrosis, atrophy), and lymphoid infiltrate (ie, aggregates and follicles) were evaluated. Lymphoid infiltrate in posttreatment biopsies revealing monotonous infiltrates of centrocyte like cells and/or LELs was judged as histologic residual lymphoma. In the following, histologic residual lymphoma is referred to as histologic residual disease (RD).

Remission Evaluation Following Hp Eradication

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

Patients with NC and PR after were referred for alternative treatment; patients diagnosed as CR were followed-up further and scored as i) continuous complete remission (CCR) when normalization of macroscopic findings continued and all follow-up biopsies revealed the histologic criteria of CR; as ii) histologic RD when normalization of macroscopic findings were persistent but in further follow-up biopsies histologic evidence of lymphoma was present; or iii) as relapse, when macroscopic and microscopic evidence of lymphoma was present.

Molecular Analyses

DNA isolation for monoclonality studies and RNA isolation from frozen and paraffin-embedded gastric biopsies for translocation t(11;18) and sequencing were performed as described previously.[7,13,19] B-cell clonality was analyzed by means of a semi-nested PCR protocol for the rearranged immunoglobulin heavy chain variable region (IgH).[13] Presence of a distinct single band was considered to be diagnostic for monoclonality. Translocation t(11;18, q21;q21) was detected by reverse-transcription PCR (RT-PCR) of the API2-MALT1 transcript from RNA samples extracted from archival paraffin-embedded tissue.[19] All molecular results were collected without reference to the clinical and histologic data.

Statistical Analysis

The Kaplan-Meier method was used to estimate survival and remission duration. Fisher's exact test (two-tailed) was used to test for differences in clinical outcome between cases with and without t(11;18) and cases with and without ongoing monoclonality. Statistical analysis was performed with SPSS (SPSS GmbH, Munich, Germany) for Windows and StatXact-6 (Cytel Software, Cambridge, MA,) .

RESULTS

Hp Eradication

Cure of *Hp* infection was achieved after the first treatment course in 116 patients (97%); four patients needed a second treatment for successful eradication.

Remission Induction

In 96 of 120 patients (80%), CR was achieved by eradication of *Hp* (Fig 1). First CR was diagnosed between 1 month and 28 months after start of the eradication treatment. The majority of the patients (59 of 96; 61%) achieved CR within the first 3 months following treatment. A further 25 patients achieved CR in the first year. For the remaining 12 patients, reaching CR took up to 28 months; these had all normalization of macroscopic findings within the first 6 months but revealed prolonged histologic residuals of lymphoma before CR was diagnosed. The follow-up of single patients is illustrated (Fig 2).

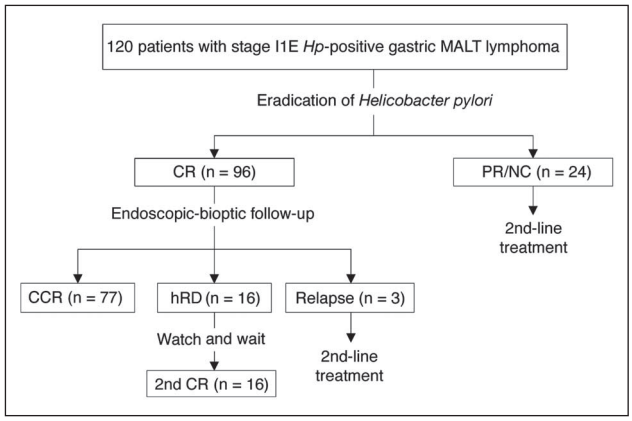

Fig 1. Response and follow-up of the 120 study patients, on the basis of macroscopical and histologic findings. *Hp, Helicobacter pylori*; MALT, mucosa-associated lymphoid tissue; CR, complete remission; PR, partial remission; NC, no change; CCR, continuous complete remission; hRD, histologic residual disease.

Twenty-four of 120 patients were classified either as NC (n = 11) or PR (n = 13) in terms of eradication therapy. During follow-up, eight of these patients revealed components of diffuse large B-cell lymphoma; one patient showed T-cell lymphoma but no GML on histologic and immunohistologic evaluation of the gastrectomy specimen.

Overall Survival

The estimated percentage of patients surviving at least 5 years is 90% (Kaplan-Meier analysis; Fig 3). All deaths, regardless of cause, were considered as events, making this a conservative estimate of survival from GML. The median follow-up for all patients is 75 months (range, 1.5 to 116 months). A total of 13 patients have died. Two patients with NC died as a result of progressive lymphoma (diffuse large B-cell lymphoma and T-cell lymphoma; survival time, 6 months and 33 months, respectively). Other causes of death were metastatic colorectal cancer (n = 1), stroke (n = 3), and heart failure (n = 6). The cause of death in one patient (85 years of age) is unknown.

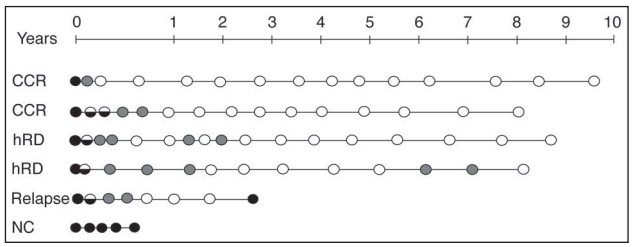

Fig 2. Follow-up of single patients. Black circles represent macroscopic and microscopic disease; black and white circles partial macroscopic remission; gray circles normalization of macroscopic findings but histologic residual disease; and white circles complete macroscopic and histologic remission. CCR, continuous complete remission; hRD, histologic residual disease; NC, no change.

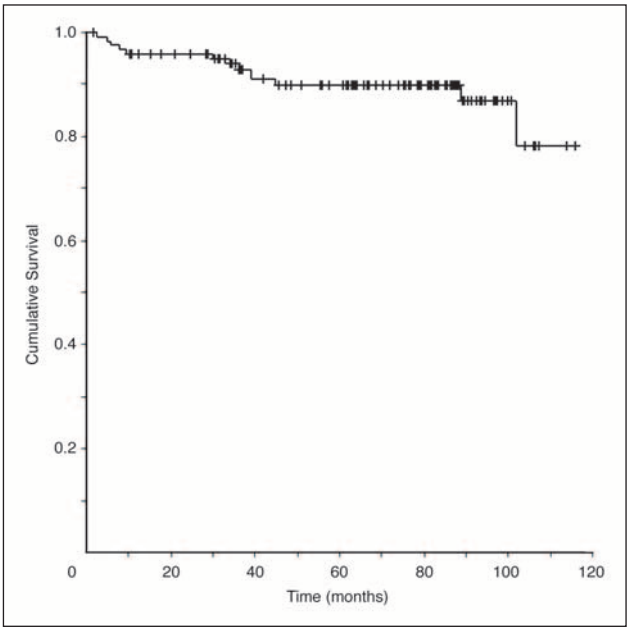

Fig 3. A Kaplan-Meier analysis was performed to analyze the cumulative survival for all 120 patients. Deaths were treated as events. Final follow-up as the cutoff date is indicated by a cross.

Duration of Remission in 96 Complete Responders

The estimated percentage of patients assessed as in CCR after 5 years is 71% (95% CI, 61% to 81%; Kaplan-Meier analysis; Fig 4). Because of different lengths of follow-up, we actually observed 44 patients who were in CCR for at least 5

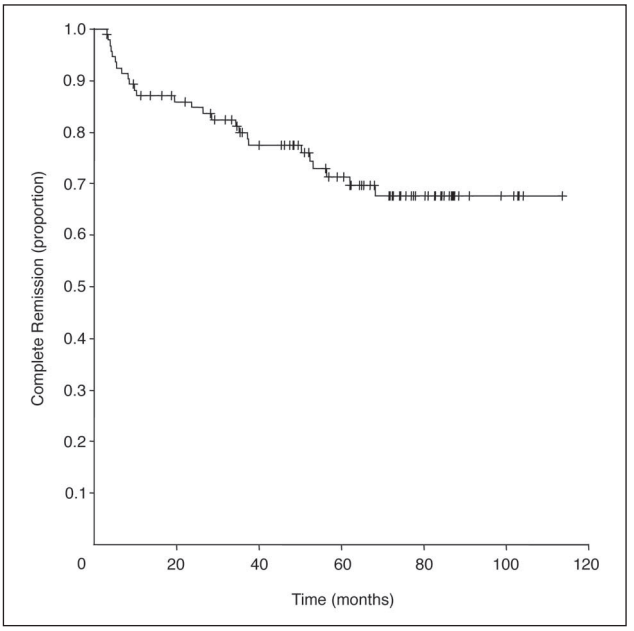

Fig 4. Duration of complete remission (CR) on the basis of histologic findings. Remissions were calculated from the first day of CR. Twenty-six events (ie, relapse, histologic residual disease, deaths) were observed after a first CR. CR was calculated using the Kaplan-Meier method.

years (range, 61 to 114 months; median, 83 months). After 114 months, the estimated percentage of patients in CCR is 68% (95% CI, 57% to 79%).

A macroscopic relapse was diagnosed in three of 96 *Hp*-negative patients (3%) within 4 months, 5 months, and 24 months, respectively, after lymphoma remission; these patients were referred for alternative treatment [operation (n = 2) or radiotherapy (n = 1)]. Before the diagnosis of relapse, one of these patients was diagnosed with *Hp* re-infection and successful re-eradication of *Hp* was performed.

Histologic RD was seen in 16 of 96 patients (17%) after three to 68 months (median, 48 months) in CR; LELs were seen in 11 of these patients. RD was present in two or more follow-up investigations in five patients, and three of these patients showed fluctuations between histologic RD and CR over a period between 3 months and 19 months. A watch-and-wait strategy was applied as described by Fischbach et al.[24] All 16 patients with histologic RD entered into a second histologic CR with a median duration of 32 months (range, zero to 101 months). In the event-free survival analysis, macroscopic relapse, histologic RD, and deaths (seven of 96, none of them related to the GML) were referred to as events (Fig 4).

Another 28 of 96 CR patients were lost for further endoscopic follow-up after a median time of 34 months (range, three to 52 months). In the event-free survival analysis, these were treated as censored at the last endoscopic follow-up date. In 13 of these patients, clinical follow-up was possible, and none exhibited a clinical hint of lymphoma relapse after a median follow-up of 69 months (range, 33 to 104 months). Fifteen patients were completely lost to follow-up and did not respond to repeated invitations to control examinations.

IgH PCR at Diagnosis and During Follow-Up

Sufficient material was available from 91 patients at diagnosis to study IgH gene rearrangement (Fig 5). Of these, 69 of 91 patients (76%) were MC, and 22 patients (24%) showed a polyclonal pattern. In 66 of the 69 MC patients, molecular follow-up was possible.

Fifty-two patients revealing CR and a MC PCR product at diagnosis were followed up for a median time of 63 months (range, five to 107 months; Fig 5). Of these, 14 patients (27%) showed ongoing monoclonality during a median follow-up period of 46 months (range, eight to 101 months), and 38 patients (73%) shifted towards polyclonality (PC). Shift to PC was diagnosed after two consecutive polyclonal PCR results, six patients showed PC in single investigations during ongoing monoclonality. The median interval from histologic CR to the first polyclonal PCR result was 28 months (range, zero to 86 months).

In five patients with a follow-up between 56 months and 101 months, the last MC amplification was sequenced and compared with the original lymphoma sample. In two of the five patients, there was no clonal relationship with the original lymphoma clone. Likewise, in another patient with a MC PCR result after 90 months of ongoing PC, no clonal relationship with the original lymphoma clone was seen.

All analyzed patients with PR or NC (n = 14) and all patients with relapse (n = 3) showed ongoing monoclonality.

Among the 52 patients in CR who were available for molecular follow-up, a relapse or the diagnosis of histologic RD was significantly more likely during ongoing monoclonality, while patients who shifted to PC were more likely to stay in CCR ($P = .0007$; relative risk, 6.30; 95% CI, 2.06 to 23.96). In four cases, histologic RD was diagnosed before, and in three cases after, the switch to PC.

Translocation t(11;18)

In total, 65 out of 71 lymphoma samples at diagnosis and six controls with follicular gastritis were successful for RT-PCR of the reference gene *G6PD*, and these samples were, thus, adequate for RT-PCR and analyzed for t(11;18). Ten patients with GML (15%) showed a positive result. All gastritis cases were negative. Data on translocation t(11;18), with regard to clinical behavior after *Hp* eradication, are

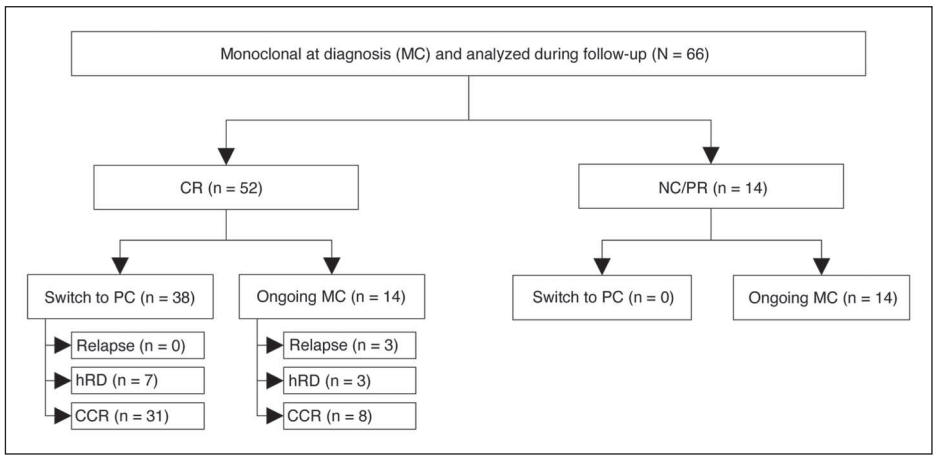

Fig 5. Analysis of B-cell clonality of gastric MALT lymphoma (GML) during follow-up. Of 120 patients, 91 patients were analyzed at diagnosis. Twenty-two patients were polyclonal (PC), and 69 patients were monoclonal (MC). CR, complete remission; NC, no change; PR, partial remission; hRD, histologic residual disease; CCR, continuous complete remission.

shown in Table 1. Patients with the translocation t(11;18; n = 10) were significantly more likely to experience a worse clinical outcome (ie, PR, NC, relapse, or histologic RD) while patients without the translocation t(11;18; n = 56) were more likely to remain in CCR ($P = .004$; relative risk, 3.02; 95% CI, 1.47 to 5.63).

Secondary Gastric Cancer

During endoscopic follow-up, early gastric adenocarcinoma was diagnosed in three patients (44 months, 47 months, and 62 months after CR of the MALT lymphoma, respectively) and completely resected by mucosectomy. All patients were in CR of both the lymphoma and the carcinoma 22 months, 34 months, and 42 months after mucosectomy, respectively.[25]

DISCUSSION

Several studies have shown that 55% to 94.7% of patients with early-stage GML will experience remission after *Hp* eradication.[9-11,26] Few data exist on the long-term stability of the remissions. We show that the majority of patients (64%) with GML achieve long-lasting remissions and have no clinical or histologic sign of relapse several years after infection eradication. These findings suggest that at least a fraction of the patients may be actually cured from their lymphoma by a therapy directed against the underlying infection only. An estimated 90% of all patients survived more than 5 years after diagnosis, and most deaths that occurred in this study were unrelated to GML; thus, survival from GML is even higher. These data are in line with a previously published study on 95 patients with a median observation period of 44.6 months and a CCR rate of 62%.[11] Our data may indicate that the CCR rate will remain at a plateau.

Another important observation is that 16 patients were classified as having histologic RD after a CR was diagnosed. Whether these patients ever had a CR before the detection of histologic RD is certainly arguable as the microscopic lesions were small and often only found in serial sections of one of multiple biopsies. Because macroscopically distinctive features at the former lymphoma site after treatment are often lacking, choosing correct areas for biopsy is difficult, and sample error is quite likely. These patients appear to have had ongoing histologic RD, which is described as minimal residual disease by Fischbach[11] and responding residual disease by Copie-Bergmann.[27]

In contrast to the approach for patients with frank macroscopic relapse, we applied a watch-and wait-strategy in the histologic RD cases. Deferred therapy has also been used in early stage follicular non-Hodgkin's lymphoma patients, with survival rates comparable with those from immediate treatment.[28] None of the histologic RD patients in our study showed progression and all, ultimately, achieved a second CR, supporting the watch-and-wait approach. The term molecular minimal residual disease is also used for ongoing B-cell clonality in GML patients in histologic CR.[10] Use of a standardized grading system for GML would help resolve what are probably semantic controversies in published studies.

So far, there were no data available whether patients with ongoing B-cell clonality have a higher risk for relapse.[9,10] Indeed, our updated results support an association between MC B-cell persistence and NC, PR, and relapse. Yet eight of 14 patients with ongoing monoclonality remained free of any indications of relapse during follow-up; one patient for more than 8 years. In a recently published paper by Noy et al[29] clonotypic PCR was used to investigate molecular remission in GML patients after involved-field radiotherapy. It is anticipated there, that with clonotypic, instead of consensus primers, a higher percentage of GML patients with ongoing monoclonality could be detected. In another study using consensus primers, prompt clearing of monoclonality after combined radiochemotherapy of gastric lymphoma is described.[30] We have addressed this question previously in three patients and found no difference with either method applied.[13] Frequency of persistent B-cell clonality decreased with longer follow-up, and no patient who had shifted to PC experienced relapse. Patients with ongoing PC might, therefore, enter a less-intense follow-up protocol with fewer endoscopies, whereas, patients with ongoing MC PCR should be monitored more closely.[13] In three of six patients followed-up beyond 5 years, the final MC PCR products were completely unrelated to the original lymphoma. They were not intraclonal variants of the original tumor clone caused by ongoing mutations but were novel clones representing unrelated clonal B-cell populations. Thus, interpretation of MC amplification should always include consideration of data from initial samples to avoid overestimations of ongoing monoclonality.

The translocation t(11;18) occurs in 24% to 48% of GMLs and is associated with resistant disease.[18-20,31] The percentage of positive cases (15%) in the present study is somewhat lower compared with these studies. The present RT-PCR approach missed 7% of rare breakpoints of

Table 1. Translocation t(11;18) and Clinical Outcome

Variable	No. t(11;18) Positive	%	No. t(11;18) Negative	%
CCR (n = 46)	3	7	43	93
PR/NC (n = 13)	3	23	10	77
RL/hRD (n = 7)	4	57	3	43
Total (n = 66)	10	15	56	85

Abbreviations: CCR, continuous complete remission; PR, partial remission; NC, no change; RL, relapse; hRD, histological residual disease.

t(11;18); however, the same protocol was used in a previous study of 138 unselected cases of GML and found the translocation in 24%, identical to the finding by Streubel et al,[32] using RT-PCR and MALT1 interphase FISH.[19] Thus, the low incidence of t(11;18) in the current cohort is most likely caused by bias towards patients at early clinical stage. Although the risk of treatment failure was significantly higher in our study for patients with detectable API2-MLT fusion transcripts, there were also three patients in ongoing CR with this marker. In a recent study, t(11;18) was not a predictive marker of response or subsequent relapse in GML patients treated with rituximab who were resistant/refractory to antibiotic treatment or not presenting with clinical evidence of *Hp* infection.[33]

A limitation of our study is that we lost 17 of 96 patients in CR to further endoscopic and clinical follow-up after a median time of 34 months, primarily because patients were symptom-free and did not agree to further follow-up. Four patients were withdrawn from further endoscopies by the referring physicians because of comorbidity and advanced age.

In 3% of patients in CR, however, eradication of *Hp* did not prevent later development of early gastric cancer. The possibility of complete resection and therefore, cure of the gastric cancer by mucosectomy strongly supports the need for long-term endoscopic follow-up in responding patients with GML.

After successful eradication, we observed one *Hp* reinfection by histology, which corresponds to published figures.[34] ^{13}C-urea breath test was not routinely done in this study. Warthin-Starry staining for detection of *Hp* as performed for all samples here was reported to have comparable sensitivity and specificity as breath-testing.[35] In addition, on histology, the grade of inflammation was assessed, which is also an important predictor of the *Hp* status.

In conclusion, long-lasting remissions occur in most GML patients after *Hp* eradication as sole treatment, and patients with histologic CCR and continuous polyclonal states may actually be cured from their disease. Histologic RD and ongoing B-cell clonality are present in a considerable number of patients. Because of the indolent course of the disease, a watch-and-wait strategy in these cases seems to be justified if close follow-up with endoscopy, endoscopic ultrasound, and histology can be performed; additional molecular studies are of unproven help.

As of now, follow-up of patients without significant comorbidities should extend beyond 5 years for detection of reinfection, relapse, and early gastric cancer.

Acknowledgment

We thank the Deutsche Krebshilfe (grant 70 2251), the Gesellschaft für Gastroenterologie in Bayern, Germany, and the Leukemia Research Fund, UK, for supporting this study. We thank all patients and their physicians for participating in this trial.

Appendix

The design of the study and the results of the first 33 patients as well as the first 50 patients have been published previously.[6,7]

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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