Long-Term Results of Anti–Helicobacter pylori Therapy in Early-Stage Gastric High-Grade Transformed MALT Lymphoma


Background: Several independent clinical studies have reported that Helicobacter pylori eradication therapy could achieve complete remission in some patients with H. pylori–positive early-stage gastric mucosa–associated lymphoid tissue (MALT) lymphomas. Methods: To compare the long-term results of anti–H. pylori therapy in early-stage, gastric low-grade and high-grade transformed MALT lymphomas, two multicenter prospective studies of anti–H. pylori therapy for early-stage gastric lymphomas conducted in Taiwan, one for low-grade MALT lymphoma, with 34 patients enrolled from March 1996 through April 1999, and one for high-grade tumors (diffuse large B-cell lymphoma with features of MALT, DLBCL[MALT] lymphoma), with 24 patients enrolled since June 1995, were directly compared. In both studies, patients generally received 2 weeks of antibiotics and had multiple sequential follow-up endoscopic examinations until complete histologic remission (CR) or disease progression; patients were monitored through January 31, 2004. CR was defined as regression of lymphoid infiltration to Wotherspoon’s score of 2 or less on all pathologic sections of endoscopic biopsy specimens. All statistical tests were two-sided. Results: The H. pylori–positive rate among the 34 low-grade patients was 94% (32 of 34). All 24 selected high-grade patients were H. pylori positive. H. pylori was eradicated in 97% (30 of 31) of evaluable H. pylori–positive low-grade patients and in 92% (22 of 24) of high-grade patients, which led to CR in 80% (24 of 30, 95% confidence interval [CI] = 65% to 95%) and 64% (14 of 22, 95% CI = 42% to 86%) of patients, respectively. None of the five patients who were either initially H. pylori negative or had persistent H. pylori infection after antibiotics achieved CR. After median follow-up of more than 5 years in complete responders, tumor recurrence was observed in three (13%) low-grade patients but not in high-grade patients. Conclusions: Anti–H. pylori therapy may be considered as one of the treatment options for early-stage H. pylori–positive gastric DLBCL(MALT), and large-scale prospective studies to validate its use as first-line therapy for such tumors should be undertaken. [J Natl Cancer Inst 2005;97:1345–53]

In 1983, Isaacsion and Wright (1) described a group of extranodal low-grade B-cell lymphomas that were derived from acquired Peyer’s patch–like structures (i.e., mucosa-associated lymphoid tissue [MALT]) in the stomach, salivary glands, lungs, and the thyroid. These MALT tumors have subsequently been recognized as a discrete group of indolent B-cell lineage lymphomas and have been classified as extranodal marginal zone lymphomas of the MALT type by the Revised European–American Lymphoma/World Health Organization (REAL/WHO) classification system (2). In the early 1990s, Wotherspoon et al. (3,4) described the high incidence of Helicobacter pylori gastritis in gastric MALT lymphoma and the histologic regression of such tumors after antibiotic therapy. Later, several independent clinical studies (5–12) demonstrated that H. pylori eradication therapy could achieve durable complete histologic remission (CR) in 56%–100% of patients with H. pylori–positive, early-stage gastric MALT lymphoma.

Eradication of H. pylori infection is well recognized as the initial therapy for early-stage gastric MALT lymphoma. However, data on the long-term outcome of patients undergoing exclusive eradication therapy are limited, more so in Asian–Pacific countries than in populations in Western countries (10,13,14).

High-grade transformed MALT lymphoma, which is generally considered to arise from H. pylori–independent clones, is thus unlikely to respond to antibiotic therapy (6,15). In addition to that suggested by reports of sporadic cases (16–26), prospective studies have shown that antibiotic therapy can also result in CR in patients with early-stage gastric high-grade transformed MALT lymphoma (27,28), which was subsequently named diffuse large B-cell lymphoma with features of MALT lymphoma (DLBCL[MALT]), according to the WHO classification system (29). Due to the limited duration of follow-up in previous studies (27,28), the potential usefulness of antibiotic therapy in gastric DLBCL(MALT) is still highly debatable (30,31).

To investigate this question, we analyzed the long-term results of antibiotic therapy in two prospective studies of Taiwanese patients.
patients with early-stage gastric MALT lymphoma and DLBCL(MALT). By monitoring the H. pylori eradication rate, CR rate, and durability of response after treatment with 2 weeks of antibiotic treatment, we hope to elucidate the therapeutic efficacy of antibiotic therapy for early-stage gastric low-grade and high-grade transformed MALT lymphoma.

**Subjects and Methods**

**Patients and Diagnostic Criteria**

T1296 study of anti–H. pylori therapy in patients with MALT lymphoma. From March 1996 through April 1999, consecutive patients with newly diagnosed stage IE or IIE-1 gastric MALT lymphoma and no prior anti–H. pylori therapy, who were first seen in or referred to clinics of participating physicians in 10 Taiwan Cooperative Oncology Group (TCOG)-affiliated hospitals, were enrolled in a study of anti–H. pylori therapy for early-stage gastric MALT lymphoma named the T1296 study. Histopathologists from individual hospitals diagnosed MALT lymphoma in accordance with criteria defined previously by Isaacson et al. (1,32), and members of the TCOG Pathology Committee, which was led by one of the authors, I. J. Su, reviewed each diagnosis. The study was approved by the institutional review board of each participating hospital and the Department of Health. Written informed consent was obtained from all patients prior to enrollment.

Prospective, multicenter study of anti–H. pylori therapy in patients with high-grade transformed MALT lymphoma, DLBCL(MALT). Starting in June 1995, a prospective study of 24 patients with newly diagnosed stage IE gastric high-grade transformed MALT lymphoma and H. pylori infection treated with antibiotics in four medical centers in Taiwan was carried out as previously described (27). All patients provided written informed consent to a brief trial of a H. pylori eradication therapy. The diagnostic criteria for high-grade transformed MALT lymphoma were those proposed by Chan et al. (29); these criteria coincided with the recommendation by the clinical advisory committee to use the WHO classification, which requires the presence of confluent clusters or sheets of large cells resembling centroblasts or lymphoblasts within a predominantly low-grade centrocyte-like cell infiltrate, or a predominance of high-grade lymphoma with only small residual low-grade foci and/or the presence of lymphoepithelial lesions (33). Patients with primary “pure” large-cell lymphoma of the stomach, without evidence of a low-grade component, were excluded. The histopathologic sections of all endoscopic biopsy specimens were reviewed independently by a hematopathologist at each institution and by the reference hematopathologist, I. J. Su. In accordance with the WHO classification, we use the term “diffuse large B-cell lymphoma with features of MALT lymphoma, DLBCL(MALT)” when describing these tumors (29).

**Therapy**

At the beginning of the DLBCL(MALT) study, the eradication regimen was amoxicillin (500 mg) and metronidazole (250 mg) four times a day, with either bismuth subcitrate (120 mg) four times a day or omeprazole (20 mg) twice a day for 4 weeks. The regimen was changed to the regimen used in T1296 MALT lymphoma study (amoxicillin [500 mg] four times a day, clarithromycin [500 mg] twice a day plus omeprazole [20 mg] twice a day for 2 weeks) after March 1996. Patients who did not respond to the T1296 regimen and patients with H. pylori reinfection were treated with second-line antibiotics at the discretion of the physician in charge.

**Evaluations**

Staging workup included a detailed physical examination, inspection of Waldeyer’s ring, computed tomography (CT) of the chest and abdomen, and small bowel series, barium enema study of the colon and rectum, and bone marrow aspiration and biopsy (34). Tumors were staged based on CT findings, according to Musshoff’s modification of the Ann Arbor staging system (35), with stage IE tumors confined to the wall of the stomach and stage IIE-1 tumors showing perigastric lymph node involvement. Endoscopic ultrasonography (EUS) examination for evaluating the depth of tumor infiltration and the status of perigastric lymph nodes was performed at the discretion of hospital facility and was optional in both studies. However, the results of EUS examination (i.e., perigastric nodal status) determined staging in the high-grade study but not in the T1296 study (in which the nodal staging was dependent on CT).

Patients were scheduled for the first follow-up upper gastrointestinal endoscopic examination 4–6 weeks after completion of antibiotic therapy, and follow-up was repeated every 3–6 months until CR was achieved or until treatment failed. At each follow-up endoscopic examination, four to six biopsy samples from the antrum and body of the stomach were evaluated for H. pylori infection, and a minimum of six biopsy samples from each of the tumors and suspicious areas were histologically evaluated. H. pylori infection status was determined by histologic examination, biopsy urease test, and bacterial culture [which was routine in the DLBCL(MALT) study but optional in the T1296 study]. Histologic features were evaluated using the scoring system described previously by Wotherspoon et al. (4). The presence of large cells was carefully evaluated. CR was defined as a Wotherspoon’s score of 2 or less on every histologic section of the biopsy specimens. Partial pathologic remission (PR) was defined as the presence of lesions with Wotherspoon’s score of 3 and no lesions with scores of 4 or 5 on any histologic section of biopsy specimens. Pathologic remission had to be confirmed by a second biopsy no less than 3 months later. In patients with CR, endoscopic examination of the stomach and CT of the abdomen were performed every 3–6 months for the first 12 months and every 6–12 months thereafter. MALT lymphoma patients with treatment failure (progressive disease [PD]), which was defined as the presence of histologically proven new lesions, worsening of Wotherspoon’s score from 3 or less to 4–5, or the presence of clusters or sheets of large, transformed cells, were removed from the study protocol, and further treatment of these patients was at the discretion of the physician in charge. DLBCL(MALT) patients with treatment failure, defined as grossly stable or progressive disease on follow-up endoscopic examination and/or the presence of a persistent or increasing proportion of large cells on microscopic examination, were also removed from the study protocol and referred immediately for systemic chemotherapy.

**Statistical Analysis**

Comparison of discrete variables was performed by chi-square test or Fisher’s exact test. For analysis of overall survival (OS), survival duration was defined as the interval from the date of...
registration to death from any cause. The survival distributions of relapse-free survival (RFS) were calculated from the date of first documentation of CR to the date of histologic confirmation of recurrence. RFS and OS were estimated by the Kaplan–Meier method (36) and compared by log-rank tests. All statistical tests were two-sided, and a value of $P$ less than .05 was considered statistically significant.

**RESULTS**

**Clinicopathologic Characteristics of Patients**

A total of 41 patients were enrolled in the T1296 MALT lymphoma study. Seven were subsequently excluded from the study because of Wotherspoon score less than 4 ($n = 3$) (revised by the Pathology Committee), lymphoepithelioma-like carcinoma ($n = 1$), high-grade transformed MALT lymphoma ($n = 1$), suspicious secondary pulmonary MALT lymphoma or stage III disease ($n = 1$), and prior gastrectomy for MALT lymphoma ($n = 1$). Although patients with stage IIE-1 MALT lymphomas were eligible for the T1296 study on the basis of abdominal CT results, all of the MALT lymphoma patients had stage IE disease. However, only $H. pylori$–positive, stage IE patients were eligible for participation in the DLBCL(MALT) study. Of the 24 DLBCL(MALT) patients (of whom data for 16 were previously reported (27)), 13 had predominantly low-grade tumors with apparent foci of clusters or sheets of large cells and 11 had frank diffuse large-cell lymphoma with features of MALT lymphoma (foci of centrocyte-like cells and/or lymphoepithelial lesions). The depth of lymphoma involvement in the gastric wall was determined by EUS in 37 patients (21 patients with MALT lymphoma and 16 with DLBCL[MALT]) and by histologic examination of surgically resected specimen in one DLBCL(MALT) patient.

The clinicopathologic characteristics of the 34 eligible MALT lymphoma patients and the 24 DLBCL(MALT) patients are listed in Table 1. No statistically significant differences in age, sex, endoscopic appearance, and lesion site between the two groups of patients were observed. However, among the 38 patients with known depth of tumor infiltration, statistically significantly more DLBCL(MALT) lymphomas had invaded into or beyond muscularis propria than MALT lymphomas (59% versus 14%; $P = .006$).

$H. pylori$–positive Rate and Eradication Rate After Antibiotic Therapy

The status of $H. pylori$ infection before antibiotic therapy was considered to be positive for patients with positive results on at least one $H. pylori$ detection test: the biopsy urease test, histology, or serology (in the T1296 study), or bacterial culture (in the DLBCL(MALT) study). $H. pylori$ infection status was defined as negative before therapy if results were negative on all three tests. The status of $H. pylori$ infection after antibiotic therapy was evaluated by both the biopsy urease test and histology but not by serology in the MALT lymphoma trial and by biopsy urease test, histology, and bacterial culture in the DLBCL(MALT) study.

The $H. pylori$ infection rate in the MALT lymphoma patients was 94% (32 of 34; 95% confidence interval [CI] = 80% to

### Table 1. Clinicopathologic characteristics of patients with early-stage, gastric mucosa–associated lymphoid tissue lymphoma with and without high-grade transformation*

<table>
<thead>
<tr>
<th>Clinicopathologic characteristics</th>
<th>MALT lymphoma</th>
<th>DLBCL(MALT) lymphoma</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>60 (30–84)</td>
<td>56 (21–83)</td>
<td>.893‡</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>15/19</td>
<td>9/15</td>
<td>.596‡</td>
</tr>
<tr>
<td>$Helicobacter pylori$ positive, n (%)</td>
<td>32 (94.1%)</td>
<td>24 (100%)</td>
<td>.893§</td>
</tr>
<tr>
<td>Stage IE, n (%)</td>
<td>34 (100%)</td>
<td>24 (100%)</td>
<td>1.00‡</td>
</tr>
<tr>
<td>Endoscopic features, n (%)</td>
<td></td>
<td></td>
<td>.612¶</td>
</tr>
<tr>
<td>Gastritis-like or multiple erosion on infiltrative mucosa</td>
<td>9 (29.4%)</td>
<td>8 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Ulceration or ulcerated mass</td>
<td>21 (61.8%)</td>
<td>13 (54.2%)</td>
<td></td>
</tr>
<tr>
<td>Erosions on giant nodular folds</td>
<td>1 (3.2%)</td>
<td>2 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (8.8%)</td>
<td>1 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Location of tumor(s), n (%)</td>
<td></td>
<td></td>
<td>.880¶</td>
</tr>
<tr>
<td>Antrum</td>
<td>6 (17.6%)</td>
<td>7 (28.8%)</td>
<td></td>
</tr>
<tr>
<td>Angularis</td>
<td>4 (11.8%)</td>
<td>2 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>Middle and/or lower body</td>
<td>14 (41.2%)</td>
<td>5 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>Upper body and/or fundus</td>
<td>1 (3.2%)</td>
<td>2 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>≥2 components</td>
<td>10 (29.4%)</td>
<td>8 (33.3%)</td>
<td>.006‡</td>
</tr>
<tr>
<td>Depth of gastric wall involvement, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submucosa or above</td>
<td>18/21 (85.7%)</td>
<td>7/17 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Muscularis propria or beyond</td>
<td>3/21 (14.3%)</td>
<td>10/17 (58.8%)</td>
<td></td>
</tr>
<tr>
<td>Initial pathologic features, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>34 (100%)</td>
<td>13 (54.2%)</td>
<td></td>
</tr>
<tr>
<td>MALT lymphoma with foci of large-cell aggregations</td>
<td></td>
<td>11 (45.8%)</td>
<td></td>
</tr>
</tbody>
</table>

* MALT lymphoma = lymphoma of mucosa-associated lymphoid tissue type; DLBCL(MALT) = diffuse large B-cell lymphoma with features of MALT lymphoma; CCL = centrocyte-like cells; LEL = lymphoepithelial lesion.

‡ $P$ values (two-sided) were calculated using the Student’s $t$ test.

§ $P$ values (two-sided) were calculated using Fisher’s exact test.

¶ Selected case patients, only $H. pylori$–positive patients were eligible.

|| $P$ values (two-sided) were calculated using one-way analysis of variance.

* Gastric wall involvement was evaluated in 38 patients in total. Evaluation was by endoscopic ultrasonography in 37 patients and by histologic examination of surgical specimen in one high-grade DLBCL(MALT) patient.
Table 2. Results of anti-\textit{Helicobacter pylori} therapy in early-stage, gastric mucosa-associated lymphoid tissue lymphoma with and without high-grade transformation*

<table>
<thead>
<tr>
<th>Clinicopathologic characteristics</th>
<th>MALT lymphoma</th>
<th>Low-grade predominant</th>
<th>DLBCL(MALT) lymphoma</th>
<th>Subtotal</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>34</td>
<td>13</td>
<td>11</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>(H. \text{ pylori} –) positive rate</td>
<td>94.1% (32/34)</td>
<td>100% (13/13)†</td>
<td>100% (11/11)†</td>
<td>100% (24/24)†</td>
<td></td>
</tr>
<tr>
<td>Eradication rate</td>
<td>96.8% (30/31)‡</td>
<td>84.6% (11/13)</td>
<td>100% (11/11)</td>
<td>91.7% (22/24)</td>
<td>.418 §</td>
</tr>
<tr>
<td>CR rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All evaluable patients</td>
<td>72.7% (24/33)</td>
<td>53.8% (7/13)</td>
<td>63.6% (7/11)</td>
<td>58.3% (14/24)</td>
<td>.263 §</td>
</tr>
<tr>
<td>Initially (H. \text{ pylori} –) positive patients</td>
<td>77.4% (24/31)</td>
<td>53.8% (7/13)</td>
<td>63.6% (7/11)</td>
<td>58.3% (14/24)</td>
<td>.134 §</td>
</tr>
<tr>
<td>(H. \text{ pylori} –) eradicated patients</td>
<td>80.0% (24/30)</td>
<td>63.6% (7/11)</td>
<td>63.6% (7/11)</td>
<td>63.6% (14/22)</td>
<td>.196 §</td>
</tr>
<tr>
<td>(H. \text{ pylori} –) persistent patients</td>
<td>0% (0/1)</td>
<td>63.6% (7/11)</td>
<td>63.6% (7/11)</td>
<td>63.6% (14/22)</td>
<td>.196 §</td>
</tr>
<tr>
<td>Initially (H. \text{ pylori} –) negative patients</td>
<td>0% (0/2)</td>
<td>63.6% (7/11)</td>
<td>63.6% (7/11)</td>
<td>63.6% (14/22)</td>
<td>.196 §</td>
</tr>
<tr>
<td>Depth of gastric wall involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submucosa or above</td>
<td>66.7% (12/18)</td>
<td>100.0% (3/3)</td>
<td>100.0% (4/4)</td>
<td>100.0% (7/7)</td>
<td>.137</td>
</tr>
<tr>
<td>Muscularis propria or beyond</td>
<td>33.3% (1/3)</td>
<td>33.3% (2/6)</td>
<td>25.0% (1/4)</td>
<td>30.0% (3/10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Time to CR¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI), mo</td>
<td>9.9 (6.1 to 13.7)</td>
<td>9.6 (0.0 to 20.4)</td>
<td>5.5 (0.0 to 11.2)</td>
<td>5.5 (1.2 to 9.7)</td>
<td>.994 #</td>
</tr>
<tr>
<td>Follow-up time of complete responders**</td>
<td>70.0 (63.9 to 83.6)</td>
<td>63.8 (20.0 to 79.7)</td>
<td>80.4 (18.7 to 101.4)</td>
<td>70.4 (21.7 to 86.8)</td>
<td>.878 **</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>12.5% (3/24)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>.283</td>
</tr>
</tbody>
</table>

* MALT lymphoma = mucosa-associated lymphoid tissue-type lymphoma; DLBCL(MALT) = diffuse large B-cell lymphoma with features of MALT lymphoma; CR = complete histologic remission; CI = confidence interval.
† Selected case patients.
‡ Including two patients with cure of \textit{Helicobacter pylori} after second-line antibiotic therapy.
§ \(P\) values (two-sided) were calculated using the chi-square test.
||\(P\) values (two-sided) were calculated using Fisher’s exact test.
* Only patients with cure of \textit{H. pylori} after antibiotic therapy were included.
** For complete responders only; comparison between MALT lymphoma and subtotal of DLBCL(MALT).

**MALT lymphoma = mucosa-associated lymphoid tissue-type lymphoma; DLBCL(MALT) = diffuse large B-cell lymphoma with features of MALT lymphoma; CR = complete histologic remission; CI = confidence interval.

Overall, the CR rate in 52 patients from whom \textit{H. pylori} was eradicated (MALT lymphoma in 30 and DLBCL[MALT] in 22) and in five patients (MALT lymphoma in three and DLBCL[MALT] in two) with either initially negative \textit{H. pylori} infection (n = 2) or persistent \textit{H. pylori} infection after antibiotic therapy (n = 3) was 73\% (38; 95\% CI = 61\% to 86\%) and 0\%, respectively (\(P = .003\)). Among \textit{H. pylori}–eradicated patients, the CR rate of those with MALT lymphoma was 80\% (24 of 30; 95\% CI = 65\% to 95\%), compared with 64\% (14 of 22; 95\% CI = 42\% to 86\%) in those with DLBCL(MALT) (\(P = .196\)) (Table 2). For the latter group, the CR rate was 64\% (7 of 11) in patients with either foci of large cell clusters in predominantly low-grade tumors or predominantly high-grade tumors with features of MALT lymphoma. The median time to CR after the completion of antibiotic therapy in \textit{H. pylori}–eradicated patients was 10 months (95\% CI = 6 to 14 months) for MALT lymphoma and 6 months (95\% CI = 1 to 10 months) for DLBCL(MALT) (\(P = .994\)).

The results of Kaplan–Meier analyses for time to CR in \textit{H. pylori}–eradicated patients are shown in Fig. 1, which shows that 25\% (6 of 24) of patients with MALT lymphoma and 7\% (1 of 14) of patients with DLBCL(MALT) achieved CR within 12–25 months after therapy. Among the 14 patients with DLBCL(MALT) who achieved CR, gross tumor regression and histologic regression of the large-cell component were evident in all at the first follow-up endoscopic examination; a sample case is shown in Fig. 2. Eight of the nine patients with unresponsive or progressive DLBCL(MALT) were referred immediately for systemic chemotherapy, which consisted mainly of cyclophosphamide, doxorubicin, vincristine, and prednisolone, and all achieved CR. The ninth patient, who had only residual low-grade tumor after antibiotic treatment, refused further therapy and was lost to follow-up.

Overall, the CR rate among patients with tumors that were limited to mucosa/submucosa and those extending into the muscularis propria or beyond was 76\% (19 of 25) and 30\% (4 of 13), respectively (\(P = .013\)). Among patients with cure of \textit{H. pylori} infection after antibiotic therapy, the CR rate of MALT lymphoma that were limited to the mucosa or submucosa and those extending into the muscularis propria or beyond was 67\% (12 of 18) and 33\% (1 of 3), respectively (\(P = .495\)); that of DLBCL(MALT) was 100\% (7 of 7) and 30\% (3 of 10), respectively (\(P = .02\)).
Follow-up

On January 31, 2004, the median follow-up time (calculated from the date of registration to either the date of death or loss of follow-up, or January 31, 2004) was 70 months (95% CI = 65 to 81 months) for patients with MALT lymphoma and 56 months (95% CI = 20 to 80 months) for patients with DLBCL(MALT). Only one lymphoma-related death occurred (due to sepsis after chemotherapy for an 80-year-old patient with intraabdominal low-grade lymphoma), and five non–lymphoma related deaths occurred [three patients with MALT lymphoma and two with DLBCL(MALT) as a result of pneumonia with respiratory failure (n = 3, aged 89, 85, and 73 years), of fulminant hepatitis secondary to hepatitis B virus reactivation (n = 1), and of two patients with DLBCL(MALT) as a result of pneumonia at the age of 85 and the other of fulminant hepatitis secondary to hepatitis B virus reactivation (n = 1)]. No high-grade transformation of MALT lymphoma was noted during the study. The 5- and 7-year cumulative survival rates of patients with MALT lymphoma were 94% (95% CI = 79% to 99%) and 87% (95% CI = 73% to 97%), respectively, whereas those of patients with DLBCL(MALT) was 92% (95% CI = 73% to 99%) and 92% (95% CI = 73% to 99%), respectively. The overall survival curves of all evaluable patients in both groups are shown in Fig. 3 (P = .994 [two-sided, calculated using the log-rank test]).

DISCUSSION

This is the first direct comparison, to our knowledge, of two prospective studies of the efficacy of H. pylori eradication in the treatment of early-stage MALT lymphoma and DLBCL(MALT) of the stomach. Our results demonstrate that the therapeutic efficacies (i.e., H. pylori eradication rate, CR rate, and durability of remission) of antibiotics for stage IE gastric high-grade transformed MALT lymphoma are similar to their efficacies in stage IE low-grade lymphomas.

In this study, we found that the H. pylori infection rate in patients with early-stage MALT lymphoma in Taiwan was 94%, which was comparable to the 92% in the previous study of Wotherspoon et al. and similar to the 73%–85% range in three prospective studies from Western countries and Japan. However, the high percentage of enrollment of ineligible patients (7 of 41, 17%) into the T1296 study was caused mainly by overinterpretation of lymphoid infiltration or by misreading of certain critical histologic features (high-grade tumor and adenocarcinoma) in these patients during the early phase of the study. This diagnostic error rate is similar to that observed by Ruskoné-Fourmestraux et al., in which 25% (16 of 64) of enrolled patients were not eligible and 14 of these had an initial diagnostic error. The findings, i.e., the existence of diagnostic error, highlight the importance of having a pathology committee thoroughly review the histologic material and check the diagnosis in a multicenter study.

Although only 33 evaluable patients were included in the T1296 study, this study is one of the largest long-term, prospective studies on H. pylori eradication therapy in MALT lymphoma patients from Asia, with a median follow-up of more than 5 years. The findings of 97% eradication rate after antibiotic therapy, 80% CR rate after cure of H. pylori infection, median of 6.7 months to CR in complete responders, 8% local relapse rate in CR patients, and the low CR rate in initially H. pylori–negative or H. pylori–persistently infected patients are all consistent with findings in previous reports from Western countries and from other Asian countries.

Among clinicopathologic factors, only depth of tumor invasion was statistically significantly different between MALT lymphoma and DLBCL(MALT) (involvement of muscularis antibiotic therapy. One patient had intraabdominal recurrence at the mesenteric lymph nodes without gastric relapse 49 months after CR. All DLBCL(MALT) patients with CR remained lymphoma free during the study, but one developed metastatic non–small-cell lung cancer.

The median follow-up time after CR (calculated from the date of first pathologic CR to either the date of tumor relapse or January 31, 2004) for patients in the MALT lymphoma and DLBCL(MALT) groups with CR was 62 months (95% CI = 54 to 68 months) and 63 months (95% CI = 15 to 78 months), respectively. The relapse-free Kaplan–Meier survival curves for both groups are shown in Fig. 4 (P = .218). Six of the eight patients with DLBCL(MALT) who achieved CR after systemic chemotherapy remained disease free, whereas the other two died—one of pneumonia at the age of 85 and the other of fulminant hepatitis secondary to hepatitis B virus reactivation 6 months after completion of chemotherapy without relapse of lymphoma.
propria or beyond in 14% and 59%, respectively; \( P = .006 \); age and sex distribution of patients, endoscopic appearances, and location of tumors were similar. Our results showed that eradication of \( H. \text{pylori} \) infection could result in CR in patients with stage IE gastric lymphomas with MALT features regardless of their histologic grading (Table 2): 64% (14 of 22; 95% CI = 42% to 86%) for DLBCL(MALT) and 80% (24 of 30; 95% CI = 65% to 95%) for MALT lymphoma (\( P = .196 \)). These results are consistent with the observation in patients with DLBCL(MALT) that the increasing proportion of large cells does not affect the response of high-grade transformed tumor to antibiotic therapy (which was 64% [7 of 11] in \( H. \text{pylori} \)-eradicated patients with foci of large cell clusters in predominantly low-grade tumors and also 64% [7 of 11] in \( H. \text{pylori} \)-eradicated patients with predominantly high-grade tumors with centrocyte-like cells and/or lymphoepithelial lesions). All 14 DLBCL(MALT) patients with CR remained relapse-free after a median follow-up of 63 months (95% CI = 15 to 78 months). As for the potentially aggressive nature of diffuse large B-cell lymphoma (the terminology recommended by the WHO advisory board for large cell–containing MALT lymphoma), the long-term relapse-free survival after eradication of \( H. \text{pylori} \) infection implies that some early-stage DLBCL(MALT) lymphomas remain \( H. \text{pylori} \) dependent and can be cured by antibiotics. These findings are consistent with those of Nakamura et al. (28) and support our previous conclusion that loss of \( H. \text{pylori} \) dependence and high-grade transformation are two separate events during the progression of MALT lymphoma of the stomach (27).

Our results showed that 20% of \( H. \text{pylori} \)-positive stage IE MALT lymphomas and one-third of DLBCL(MALT) lymphomas had lost their \( H. \text{pylori} \) dependence, i.e., they were not responsive to antibiotic therapy. Clinically, depth of tumor invasion and eradication of \( H. \text{pylori} \) infection are important factors to predict the response to antibiotic therapy (8,11,12,29). In this study, one-third of MALT lymphomas and DLBCL(MALT) lymphomas

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**Fig. 2.** An example of high-grade transformed mucosa-associated lymphoid tissue-type lymphoma responsive to antibiotic treatment. A) Before treatment, upper gastrointestinal endoscopic examination reveals an irregular ulceration with elevated, nodular margin at the angularis of the stomach, and endoscopic ultrasonography shows a homogenous hypoechoic mass infiltration of whole layers of the gastric wall (inset). \( \text{Bar} = 10 \text{~mm} \). B) Diffuse large cells and small lymphoid cells infiltrating the lamina propria are seen on histopathologic examination (hematoxylin–eosin staining [H&E], \( \times 400; \text{Bar} = 200 \mu \text{m} \)). C) Four weeks after eradication of \( H. \text{pylori} \) with 2 weeks of antibiotic treatment, the ulceration at the angularis is healed with a residual reddish scar. \( \text{Bar} = 10 \text{~mm} \). D) Biopsy shows an aggregation of small atypical lymphoid cells in the lamina propria (H&E, \( \times 200; \text{Bar} = 100 \mu \text{m} \)). E) Ten months after eradication of \( H. \text{pylori} \), grossly, a wide-based whitish scar covered with telangiectatic vessels is seen at the angularis, and endoscopic ultrasonography reveals blurring of layering and a mild thickening of the second to third layers of the gastric wall (inset). \( \text{Bar} = 10 \text{~mm} \). F) Biopsy shows infiltration of some small lymphocytes in the lamina propria (H&E, \( \times 200; \text{Bar} = 100 \mu \text{m} \)).
with deep invasion (into or beyond the muscularis propria) remained \( H. \) pylori dependent. Given the limited toxicity profiles of \( H. \) pylori eradication therapy and the durability of response, antibiotics should be considered as one of the possible first-line therapies for stage-IE \( H. \) pylori–positive gastric DLBCL(MALT), if an intensive follow-up schedule can be strictly executed. However, large-scale prospective studies are still warranted to validate the use of antibiotics as first-line therapy for such tumors.

In addition, identification of additional pathologic, molecular, and biologic markers associated with the loss of \( H. \) pylori dependence should help to tailor the therapeutic strategy for individual patients with gastric lymphoma. In recent years, the understanding of the biology of gastric MALT lymphoma has increased markedly, i.e., the findings of recurrent translocations t(11;18) (q21;q21) and t(1;14) (p22;q23) in the tumors and the association of these translocations with aberrant nuclear expression of BCL10 and NF-\( \kappa \)B in gastric MALT lymphoma (38–42). Clinically, the t(11;18) (q21;q21) translocation is an important prognostic factor to predict the response of gastric MALT lymphoma to antibiotic therapy (43). Liu et al. (44) detected t(11;18) (q21;q21) in two of 48 patients with antibiotic-responsive gastric MALT lymphomas and in 42 of the 63 patients with antibiotic nonresponsive tumors, including 26 (60%) of 43 patients with stage IE tumors. Unfortunately, t(11;18) is an uncommon event in gastric DLBCL with or without features of MALT lymphoma, which precludes its use in predicting the response of DLBCL(MALT) to antibiotics (45). However, Kuo et al. (46) recently examined the expression and distribution of BCL10 and NF-\( \kappa \)B in stage IE gastric DLBCL(MALT) patients who were treated with antibiotics as first-line therapy and found that nuclear expression of both BCL10 and NF-\( \kappa \)B was significantly more frequent in the \( H. \) pylori–independent tumors than in the \( H. \) pylori–dependent tumors. Abrupt nuclear expression of BCL10 and NF-\( \kappa \)B was generally detected in both the large cells and their low-grade counterparts within the \( H. \) pylori–independent tumor. This finding indicates that nuclear expression of BCL10 and NF-\( \kappa \)B may be associated with the \( H. \) pylori–independent status not only of early-stage gastric DLBCL(MALT) but also of early MALT lymphoma.

On the basis of our results and the findings of Kuo et al. (46), we have recently designed a biologic marker–tailoring prospective study for stage IE, \( H. \) pylori–positive gastric DLBCL(MALT). Our goal is to treat patients whose tumors lack nuclear expression of NF-\( \kappa \)B with antibiotics as first-line therapy and to randomly assign patients whose tumors have nuclear expression of NF-\( \kappa \)B to first-line treatment with either antibiotics or standard front-line chemotherapy (i.e., cyclophosphamide, doxorubicin, vincristine, and prednisolone, with or without rituximab). Patients with tumors that fail to respond to first-line antibiotics will be immediately referred to chemotherapy. The study will prospectively evaluate the efficacy of antibiotics in terms of response rate and time to tumor progression, the predictive value of NF-\( \kappa \)B expression pattern on \( H. \) pylori dependence, and the efficacy of standard chemotherapy for NF-\( \kappa \)B nuclear staining–positive and/or \( H. \) pylori eradication treatment nonresponsive stage IE gastric DLBCL(MALT).

In summary, this study has clearly demonstrated the long-term efficacy of antibiotic therapy in \( H. \) pylori–positive stage IE DLBCL(MALT) lymphoma of the stomach. The more than 60% CR rate in patients with diffuse large B-cell lymphoma (with features of MALT lymphoma) after \( H. \) pylori eradication, and the more than 5 years of median relapse-free survival in these patients, implies that antibiotic therapy should be considered a treatment option for \( H. \) pylori–positive stage IE gastric DLBCL(MALT).

**REFERENCES**


NOTES

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