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

Li-Tzong Chen, Jaw-Town Lin, John Jen Tai, Gran-Hum Chen, Hong-Zen Yeh, Sheng-Shun Yang, Hsiu-Po Wang, Sung-Hsin Kuo, Bor-Shyang Sheu, Chang-Ming Jan, Wen-Ming Wang, Tsang-En Wang, Chew-Wun Wu, Chi-Long Chen, Ih-Jen Su, Jacqueline Whang-Peng, Ann-Lii Cheng

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) lymphoma.** ***Methods:*** **To compare the long-term results of anti–*H. pylori* therapy in early-stage, gastric low-grade and high-grade transformed MALT lymphoma, two multicenter prospective studies of anti–*H. pylori* therapy for early-stage gastric lymphoma conducted in Taiwan, one for low-grade MALT lymphoma, with 34 patients enrolled from March 1996 through April 1999, and one for high-grade transformed 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, Isaacson 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

Affiliations of authors: Divisions of Cancer Research (L-TC, JW-P), Biostatistics and Bioinformatics (JJT), and Clinical Research (I-JS), National Health Research Institutes, Taipei; Taiwan; Departments of Internal Medicine (J-TL, A-LC), Emergency Medicine (H-PW), and Oncology (S-HK, A-LC), National Taiwan University Hospital, Taipei, Taiwan; Division of Biostatistics, Institute of Epidemiology, National Taiwan University, Taipei, Taiwan (JJT); Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan (G-HC, H-ZY, S-SY); Division of Gastroenterology, Department of Internal Medicine, National Cheng-Kung University Hospital, Tainan, Taiwan (B-SS); Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (L-TC, C-MJ, W-MW); Division of Gastroenterology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan (T-EW); Department of Surgery, Veterans General Hospital, Taipei, Taiwan (C-WW); Department of Pathology, Taipei Medical University Hospital, Taipei, Taiwan (C-LC).

Correspondence to: Dr. Li-Tzong Chen, MD, PhD, Division of Cancer Research, National Health Research Institutes, Taipei, Taiwan (e-mail: leochen@nhri.org.tw).

See "Notes" following "References."

DOI: 10.1093/jnci/dji277

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 specimens 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 lymphoma 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*

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

*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–*Helicobacter pylori* therapy in early-stage, gastric mucosa–associated lymphoid tissue lymphoma with and without high-grade transformation*

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

*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 *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 *H. pylori* after antibiotic therapy were included.

#*P* values (two-sided) were calculated using Kaplan–Meier analysis with log-rank test.

**For complete responders only; comparison between MALT lymphoma and subtotal of DLBCL(MALT).

99%), whereas the infection rate was 100% (24 of 24) in the DLBCL(MALT) patients because *H. pylori* positivity was required for eligibility. One female patient with MALT lymphoma who underwent subtotal gastrectomy 2 weeks after antibiotic therapy was excluded from evaluation of *H. pylori* eradication status and tumor response. Eradication of *H. pylori* infection was achieved in 97% (30 of 31; 95% CI = 83% to 100%; after first-line treatment in 28 and after second-line treatment in two) of patients with MALT lymphoma who completed the study protocol and in 92% (22 of 24; 95% CI = 73% to 99%) of patients with DLBCL(MALT). The histology of DLBCL(MALT) of the two patients with persistent *H. pylori* infection after antibiotic therapy was predominantly MALT lymphoma with foci of clusters or sheets of large cells.

Tumor Response

Overall, the CR rate in 52 patients from whom *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 *H. pylori* infection (n = 2) or persistent *H. pylori* infection after antibiotic therapy (n = 3) was 73% (38; 95% CI = 61% to 86%) and 0%, respectively (*P* = .003). Among *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 *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 *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 *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).

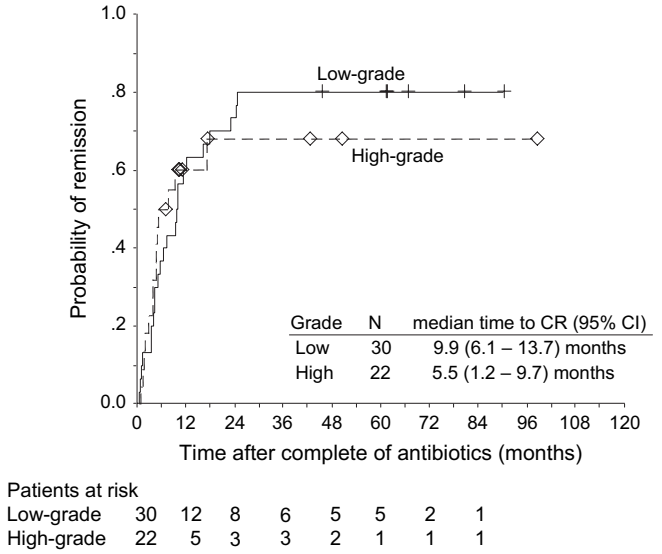

Fig. 1. Time to complete histologic remission (CR) of *Helicobacter pylori*–eradicated patients, calculated from the completion of antibiotic therapy to first evidence of CR by Kaplan–Meier analysis, low-grade (lymphoma of mucosa-associated lymphoid tissue type, MALT lymphoma, **solid line**) versus high-grade (diffuse large B-cell lymphoma with features of MALT lymphoma, DLBCL[MALT], **dashed line**) tumors, $P = .994$ (two-sided, calculated using the log-rank test).

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 6 months after completion of chemotherapy (n = 1), and of metastatic adenocarcinoma of unknown origin (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 ($P = .982$).

The median follow-up time for complete responders among patients with MALT lymphoma and DLBCL(MALT) was 70 months (95% CI = 64 to 84 months) and 70 months (95% CI = 22 to 87 months), respectively. Relapse occurred in three (13%) of 24 MALT lymphoma and 0 of 24 DLBCL(MALT) patients who achieved complete remission ($P = .283$). Two (8%) MALT lymphoma patients had local lymphoma recurrence after 7.7 months and 23 months. *H. pylori* reinfection was noted in the latter patient that occurred 6 months before histologic evidence of tumor recurrence. The *H. pylori* reinfections and the relapsed tumors were not responsive to subsequent second- or third-line 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.

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 of the stomach in Taiwan was 94%, which was comparable to the 92% in the previous study of Wotherspoon et al. *(3)* and similar to the 73%–85% range in three prospective studies from Western countries and Japan *(8,11,37)*. 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. *(11)*, 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 *(5–13,37)*.

Among clinicopathologic factors, only depth of tumor invasion was statistically significantly different between MALT lymphoma and DLBCL(MALT) (involvement of muscularis

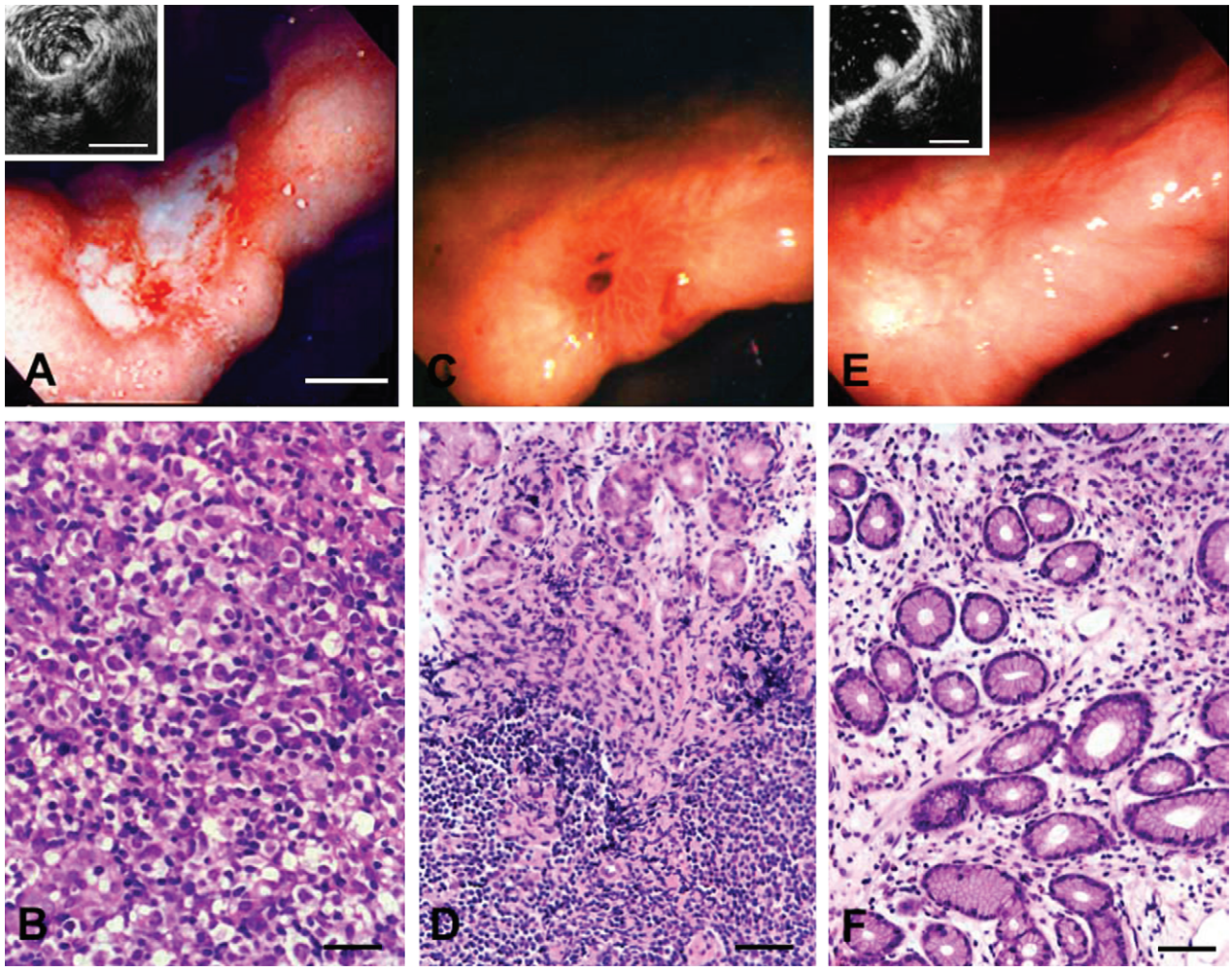

Fig. 2. An example of high-grade transformed mucosa-associated lymphoid tissue-type lymphoma responsive to antibiotic treatment. **A**) Before treatment, upper gastrointestinal endoscopic examination reveals an irregular ulceration with elevated, nodular margin at the angularis of the stomach, and endoscopic ultrasonography shows a homogenous hypoechoic mass infiltration of whole layers of the gastric wall (**inset**). **Bar** = 10 mm. **B**) Diffuse large cells and small lymphoid cells infiltrating the lamina propria are seen on histopathologic examination (hematoxylin–eosin staining [H&E], ×400; **Bar** = 200 μm). **C**) Four weeks after eradication of *Helicobacter pylori* with 2 weeks of antibiotic treatment, the ulceration at the angularis is healed with a residual reddish scar. **Bar** = 10 mm. **D**) Biopsy shows an aggregation of small atypical lymphoid cells in the lamina propria. Neither large blast cells nor lymphoepithelial lesions were seen (H&E, ×200; **Bar** = 100 μm). **E**) Ten months after eradication of *H. 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**). **Bar** = 10 mm. **F**) Biopsy shows infiltration of some small lymphocytes in the lamina propria (H&E, ×200; **Bar** = 100 μm).

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. 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. pylori*–eradicated patients with foci of large cell clusters in predominantly low-grade tumors and also 64% [7 of 11] in *H. 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. pylori* infection implies that some early-stage DLBCL(MALT) lymphomas remain *H. 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. 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. pylori*–positive stage IE MALT lymphomas and one-third of DLBCL(MALT) lymphomas had lost their *H. pylori* dependence, i.e., they were not responsive to antibiotic therapy. Clinically, depth of tumor invasion and eradication of *H. 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

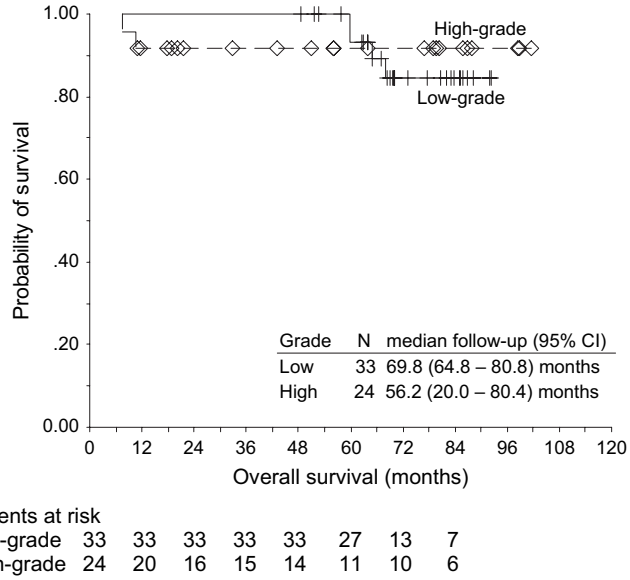

Fig. 3. Overall survival of patients with early-stage gastric lymphoma with antibiotics as first-line therapy. Low-grade (lymphoma of mucosa-associated lymphoid-tissue type, MALT lymphoma, **solid line**) versus high-grade (diffuse large B-cell lymphoma with features of MALT lymphoma, DLBCL[MALT], **dashed line**), $P = .982$ (two-sided, calculated using the log-rank test).

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.

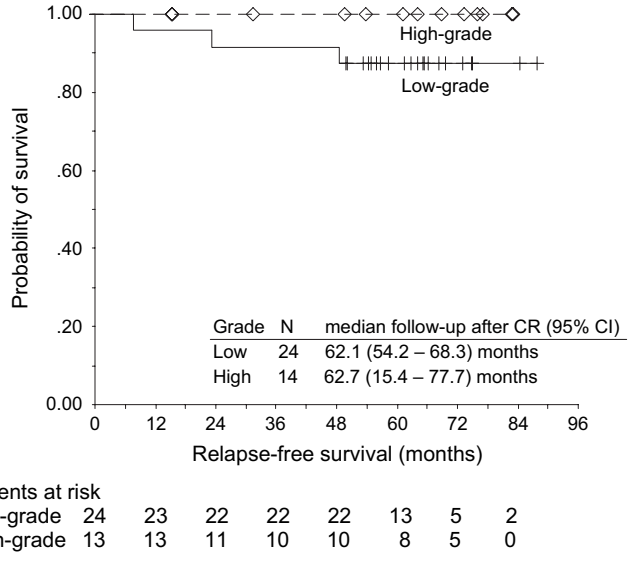

Fig. 4. Relapse-free survival of patients with early-stage gastric lymphoma. Patients with low-grade (lymphoma of mucosa-associated lymphoid-tissue type, MALT lymphoma, **solid line**) versus those with high-grade (diffuse large B-cell lymphoma with features of MALT lymphoma, DLBCL[MALT], **dashed line**) tumors who achieved complete histologic remission after antibiotic therapy, $P = .218$ (two-sided, calculated using the log-rank test).

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-κB 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-κB 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-κB was statistically significantly more frequent in the *H. pylori*–independent tumors than in the *H. pylori*–dependent tumors. Aberrant nuclear expression of BCL10 and NF-κB 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 or NF-κB 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 Kou 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-κB with antibiotics as first-line therapy and to randomly assign patients whose tumors have nuclear expression of NF-κB 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-κB expression pattern on *H. pylori* dependence, and the efficacy of standard chemotherapy for NF-κB nuclear staining–positive and/or *H. pylori* eradication treatment nonresponding 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

(1) Isaacson PG, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinct type of B-cell lymphoma. Cancer 1983;82: 1410–6.

(2) A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma: the non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909–18.
(3) Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori associated gastritis and primary B-cell gastric lymphoma. Lancet 1991;338:1175–6.
(4) Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, 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.
(5) Roggero E, Zucca E, Pinotti G, Pascarella A, Capella C, Savio A, 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.
(6) Neubauer A, Thiede C, Morgner A, Alpen B, Ritter M, Neubauer B, 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) Montalban C, Santon A, Boixeda D, Redondo C, Alvarez I, Calleja JL, et al. Treatment of low grade gastric mucosa-associated lymphoid tissue lymphoma in stage I with Helicobacter pylori eradication. Long-term results after sequential histologic and molecular follow-up. Haematologica 2001;86:609–17.
(8) Steinbach G, Ford R, Glober G, Sample D, Hagemeister FB, Lynch PM, et al. Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue: an uncontrolled study. Ann Intern Med 1999;131:88–95.
(9) Weston AP, Banerjee SK, Horvat RT, Zoubine MN, Campbell DR, Cherian R. Prospective long-term endoscopic and histologic follow-up of gastric lymphoproliferative disease of early stage IE low-grade B-cell mucosa-associated lymphoid tissue type following Helicobacter pylori eradication treatment. Int J Oncol 1999;15:899–907.
(10) Begum S, Sano T, Endo H, Kawamata H, Urakami Y. Mucosal changes of the stomach with low-grade mucosa-associated lymphoid tissue lymphoma after eradication of Helicobacter pylori*:* follow-up study of 48 cases. J Med Invest 2000;47:36–46.
(11) Ruskone-Fourmestaux A, Lavergne A, Aegerter PH, Megraud F, Palazzo L, de Mascarel A, et al. Predictive factors for regression of gastric MALT lymphoma after anti-Helicobacter pylori treatment. Gut 2001; 48:297–303.
(12) Fischbach W, Goebeler-Kolve ME, Dragosics B, Greiner A, Stolte M. 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.
(13) Kim YS, Kim JS, Jung HC, Lee CH, Kim CW, Song IS, et al. Regression of low-grade gastric mucosa-associated lymphoid tissue lymphoma after eradication of Helicobacter pylori: possible association with p16 hypermethylation. J Gastroenterol 2002;37:17–22.
(14) Chiang IP, Wang HH, Cheng AL, Lin JT, Su IJ. Low-grade gastric B-cell lymphoma of mucosa-associated lymphoid tissue: clinicopathologic analysis of 19 cases. J Formos Med Assoc 1996;95:857–65.
(15) Hussell T, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue to Helicobacter pylori. Lancet 1993;342:571–4.
(16) Seymour JF, Anderson R, Bhathal PS. Regression of gastric lymphoma with therapy for Helicobacter pylori infection. Ann Intern Med 1997; 127:247.
(17) Ng WW, Lam CP, Chau WK, Li FY, Huang CC, Chang FY, et al. Regression of high-grade gastric mucosa-associated lymphoid tissue lymphoma with Helicobacter pylori after triple antibiotic therapy. Gastrointest Endosc 2000;51:93–6.
(18) Alpen B, Robbecke J, Wundisch T, Stolte M, Neubauer A. Helicobacter pylori eradication therapy in gastric high grade non Hodgkin's lymphoma (NHL). Ann Hematol 2001;80 Suppl 3:B106–7.
(19) Salam I, Durai D, Murphy JK, Sundaram B. Regression of primary high-grade gastric B-cell lymphoma following Helicobacter pylori eradication. Eur J Gastroenterol Hepatol 2001;13:1375–8.
(20) Miki H, Hideo S, Harada H, Yamanoi Y, Uraoka T, Sotozono M, et al. Early stage gastric MALT lymphoma with high-grade component cured by Helicobacter pylori eradication. J Gastroenterol 2001;36:121–4.
(21) Morgner A, Miehlke S, Fischbach W, Schmitt W, Muller-Hermelink H, Greiner A, et al. Complete remission of primary high-grade B-cell gastric lymphoma after cure of Helicobacter pylori infection. J Clin Oncol 2001;19:2041–8.
(22) Montalban C, Santon A, Boixeda D, Bellas C. Regression of gastric high-grade mucosa associated lymphoid tissue (MALT) lymphoma after Helicobacter pylori eradication. Gut 2001;49:584–7.
(23) Sugimoto M, Kajimura M, Sato Y, Hanai H, Kaneko E, Kobayashi H. Regression of primary gastric diffuse large B-cell lymphoma after eradication of Helicobacter pylori. Gastrointest Endosc 2001;54:643–5.
(24) Gretschel S, Hunerbein M, Foss HD, Krause M, Schlag PM. Regression of high-grade gastric B-cell lymphoma after eradication of Helicobacter pylori. Endoscopy 2001;33:805–7.
(25) Hiyama T, Haruma K, Kitadai Y, Ito M, Masuda H, Miyamoto M, et al. Helicobacter pylori eradication therapy for high-grade mucosa-associated lymphoid tissue lymphomas of the stomach with analysis of p53 and K-ras alteration and microsatellite instability. Int J Oncol 2001;18: 1207–12.
(26) Alsolaiman MM, Bakis G, Nazeer T, MacDermott RP, Balint JA. Five years of complete remission of gastric diffuse large B cell lymphoma after eradication of Helicobacter pylori infection. Gut 2003; 52:507–9.
(27) Chen LT, Lin JT, Shyu RY, Jan CM, Chen CL, Chiang IP, et al. Prospective study of Helicobacter pylori eradication therapy in stage IE high-grade mucosa-associated lymphoid tissue lymphoma of the stomach. J Clin Oncol 2001;19:4245–51.
(28) Nakamura S, Matumoto T, Suekane H, Takeshita M, Hizawa K, Kawasaki M, et al. Predictive value of endoscopic ultrasonography for regression of gastric low-grade and high-grade MALT lymphomas after eradication of Helicobacter pylori. Gut 2001;48:454–60.
(29) Harris NL, Jaffe ES, Diebold J, Fladrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting—Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835–49.
(30) Ely S. Distinction between "high grade MALT" and diffuse large B cell lymphoma of mucosa associated lymphoid tissue. Gut 2002;51:893.
(31) Kahl BS. Update: gastric MALT lymphoma. Curr Opin Oncol 2003;15: 347–52.
(32) Isaacson PG, Spencer J. Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 1987;11:445–62.
(33) Chan JK, Ng CS, Isaacson PG. Relationship between high-grade lymphoma and low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALToma) of the stomach. Am J Pathol 1990;136:1153–64.
(34) de Jong D, Aleman BM, Taal BG, Boot H. Controversies and consensus in the diagnosis, work-up and treatment of gastric lymphoma: an international survey. Ann Oncol 1999;10:275–80.
(35) Musshoff K. Klinische Stadieneinteilung der nicht-Hodgkin Lymphome. Strahlenthreapie Onkol 1977;153:218–21.
(36) Kaplan ER, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–81.
(37) Nakamura T, Inagaki H, Seto M, Nakamura S. Gastric low-grade B-cell MALT lymphoma: treatment, response, and genetic alteration. J Gastroenterol 2003;38:921–9.
(38) Ye H, Liu H, Raderer M, Chott A, Ruskone-Fourmestraux A, Wotherspoon A, et al. High incidence of t(11;18) (q21;q21) in Helicobacter pylori-negative gastric MALT lymphoma. Blood 2003;101:2547–50.
(39) Rosenwald A, Ott G, Stilgenbauer S, Kalla J, Bredt M, Katzenberger T, et al. Exclusive deletion of the t(11;18) (q21;q21) in extranodal marginal zone B cell lymphomas (MZBL) of MALT type in contrast to other MZBL and extranodal large B cell lymphomas. Am J Pathol 1999;155:1817–21.
(40) Willis TG, Jadayel DM, Du MQ, Peng H, Perry AR, Abdul-Rauf M, et al. Bcl10 is involved in t(1;14) (p22; q32) of MALT B cell lymphoma and mutated in multiple tumor types. Cell 1999;96:35–45.
(41) Maes B, Demunter A, Peeters B, De Wolf-Peeters C. BCL10 mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the API2-MLT fusion is associated with aberrant nuclear BCL10 expression. Blood 2002;99: 1398–404.

(42) Lucas PC, Yonezumi M, Inohara N, McAllister-Lucas LM, Abazeed ME, Chen FF, et al. Bcl10 and MALT1, Independent targets of chromosomal translocation in MALT Lymphoma, cooperate in a novel NF-κB signaling pathway. J Biol Chem 2001;276:19012–9.

(43) Alpen B, Neubauer A, Dierlamm J, Marynen P, Thiede C, Bayerdorfer E, et al. Translocation t(1;18) absent in early gastric marginal zone B-cell lymphoma of MALT type responding to eradication of Helicobacter pylori infection. Blood 2000;95:4014–5.

(44) Liu H, Ye H, Ruskone-Fourmestraux A, De Jong D, Pileri S, Thiede C, 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.

(45) Baens M, Maes B, Steyls A, Geboes K, Marynen P, De Wolf-Peeters C. The product of the t(11;18), an API2-MLT fusion, marks nearly half of gastric MALT type lymphomas without large cell proliferation. Am J Pathol 2000;156:1433–9.

(46) Kuo SH, Chen LT, Yeh KH, Wu MS, Hsu HC, Yeh PY, et al. Nuclear expression of BCL10 or nuclear factor kappa B predicts Helicobacter pylori-independent status of early-stage, high-grade gastric mucosa-associated lymphoid tissue lymphomas. J Clin Oncol 2004;22:3491–7.

NOTES

Supported by grants from the Taiwan Cooperative Oncology Group, Division of Cancer Research, National Health Research Institutes, Taipei, Taiwan.

We thank the centers and clinicians/pathologists participating in the study: National Taiwan University Hospital (Jyh-Chin Yang, I-Ping Chiang); MacKay Memorial Hospital (Shou-Chuan Shih, Shee-Chan Lin); Veterans General Hospital, Taipei (Hwai-Jeng Lin, Tseng-Shing Chen, Shiang-Ming Liu); Tri-service General Hospital (Rong-Yaun Shyu); Veterans General Hospital, Taichung (Sek-Kwong Poon, Han-Chung Lien, Guan Chou); National Cheng-Kung University Hospital (Ching-Yu Chen); Veterans General Hospital, Kaohsiung (Jin-Shiung Cheng, Ping-I Hsu); Kaohsiung Medical University Hospital (Chiang-Shin Liu, Kun-Bow Tsai). We also thank Miss Wei-Lien Feng, Bor-Rong Chen, Pei-Chyi Lin, Yung-Hsin Chin, Te-Chih Wei, Mei-Hua Lee, and Ing-Ing Luo, the research nurses of the Taiwan Cooperative Oncology Group, for their assistance in conducting this study. We also gratefully acknowledge the help of Miss Shu-Chuan Lai in data management.

Li-Tzong Chen and Ann-Lii Cheng contributed equally to this report.

Manuscript received March 26, 2005; revised July 5, 2005; accepted August 8, 2005.