REVIEW

Effects of *Helicobacter pylori* Eradication on Early Stage Gastric Mucosa–Associated Lymphoid Tissue Lymphoma

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BACKGROUND & AIMS: Different remission rates of gastric low-grade, B-cell, mucosa–associated lymphoid tissue (MALT) lymphoma have been reported after *Helicobacter pylori* eradication. We assessed the long-term remission and relapse rates of early stage MALT lymphoma in patients treated only by *H pylori* eradication and identified factors that might predict outcome. **METHODS:** This systematic review analyzed data from 32 studies, including 1408 patients. **RESULTS:** The MALT lymphoma remission rate was 77.5% (95% confidence interval, 75.3−79.7), and was significantly higher in patients with stage I than stage II_1 lymphoma (78.4% vs 55.6%; $P = .0003$) and in Asian than in Western groups (84.1% vs 73.8%; $P = .0001$). Neoplasia confined to the submucosa regressed more frequently than that with deeper invasion (82.2% vs 54.5%; $P = .0001$); patients with lymphoma localized to the distal stomach experienced regression more frequently than those with lymphoma of the proximal stomach (91.8% vs 75.7%; $P = .0037$). The remission rate was higher among patients without the *API2–MALT1* translocation than in those with this translocation (78% vs 22.2%; $P = .0001$). In an analysis of data from 994 patients, 7.2% experienced lymphoma relapse during 3253 patient-years of follow-up evaluation, with a yearly recurrence rate of 2.2%. Infection and lymphoma were cured by additional eradication therapy in all patients with *H pylori* recurrence (16.7%). Five (0.05%) of the patients initially cured of lymphoma developed high-grade lymphoma within 6 to 25 months of therapy. **CONCLUSIONS: *H pylori* eradication is effective in treating approximately 75% of patients with early stage gastric lymphoma. Long-term follow-up evaluation of these patients is needed to detect early lymphoma relapse or progression.**

Helicobacter pylori infection is the main pathogenic factor underlying development of low-grade, B-cell, mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach.[1,2] International guidelines strongly suggest bacterial eradication in all gastric MALT lymphoma patients[3–6]; disease remission occurs in more than 70% of patients when this neoplasia is treated at an early stage.[7,8]

Although the incidence of primary gastric lymphoma has increased in recent decades,[9] it remains a rare disease. Consequently, studies of the efficacy of curing *H pylori* infection in these patients are generally small and heterogeneous. Moreover, disease relapse has been reported after lymphoma remission, with or without bacterial recurrence.[1,8] Therefore, it is difficult to determine the true effects of bacterial eradication on long-term remission of MALT lymphoma. We performed a systematic review of the literature to assess the lymphoma remission rate after *H pylori* eradication and disease relapse rates after long-term follow-up periods.

Methods

Literature Search

Separate computer-assisted searches were performed using PubMed. Each search was performed on all English language articles through June 2008, using the exploded medical subject heading terms *lymphoma*, *Helicobacter pylori, therapy*, *eradication, remission*, and *follow up*. Boolean operators (NOT, AND, OR) also were used in succession to narrow and widen the search. Only studies concerning primary, low-grade, MALT lymphoma of the stomach associated with *H pylori* infection were considered; diffuse large B-cell lymphoma with features of MALT were excluded. Trials enrolling patients with either stage IE1–IE2 or IIE1 lymphoma, according to Ann Arbor classification as modified by Musshof,[10] were considered; series that also included cases staged IIE_2 or higher were excluded unless it was possible to correctly extrapolate data of a patient subgroup with early stages. In detail, these stages correspond to lymphoma confined to the gastric wall (stage I) or perigastric lymph nodes (stage IIE_1). Data of patients treated with only *H pylori* eradication were considered. Full articles of all relevant studies were retrieved, and manual searches of reference lists from identified relevant articles were performed to identify any additional studies that might have been missed. When more than one publication from the same investigator or group was available, only the most updated version, including the entire sample size, was considered for this pooled-data analysis. Studies that included pediatric or transplant patients, those published only in ab-

Abbreviations used in this paper: CI, confidence interval; MALT, mucosa-associated lymphoid tissue.

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stract form, single case reports or studies of fewer than 5 patients, reviews, and studies that were not published in English were not included in the analyses.

Data Extraction

Two investigators (A.Z. and C.H.) extracted the data from the studies that met the selection criteria. Data were extracted concerning the following: (1) number of patients treated with only *H pylori* eradication therapy, (2) number of patients in whom the infection was eradicated successfully (either directly provided or calculated), (3) number of patients who finally achieved complete remission of lymphoma (partial remission was not taken into account), and (4) number of patients with lymphoma recurrence at follow-up evaluation. *H pylori* recurrence (re-infection or recrudescence) was defined as the reappearance of bacteria after a verified eradication with different tests at least 1 month after antibiotic therapy.[11,12] Both investigators of this study approved the data extraction method and a final accord was achieved for the 2 trials with discordant data interpretation.

Statistical Analysis

The percentage and 95% confidence intervals of complete lymphoma remission after *H pylori* eradication were calculated. Data from different patient subgroups were compared by using the chi-squared test or the Fisher exact test. A P value of less than .05 was considered statistically significant.

Results

Search Results

After a thorough review of the titles, abstracts, and text of the potentially relevant studies, the full text from 79 studies of *H pylori* eradication in patients with gastric lymphoma was retrieved and evaluated. Of these, 32 trials met inclusion criteria for this pooled analysis[13–44]; 47 studies were not included (Table 1). The exclusion criteria were as follows: (1) articles that reported preliminary data provided elsewhere (29 studies), (2) articles that did not provide information about initial lymphoma stage (8 studies), and (3) studies that included patients with lymphoma stages greater than IIE_2 who had been treated with therapies beyond bacteria eradication (chemotherapy, radiotherapy, or surgery), or that did not determine remission rate according to the lymphoma stage (10 studies).

Descriptive Analysis

Of the 32 studies analyzed in this pooled-data analysis, 23 were prospective and 9 were retrospective. The analysis

Table 1. Data of Selected Studies Meeting the Inclusion Criteria

Country (study)	Study design	Patients enrolled[a]	Lymphoma stage	Follow-up period, *mo* (range)	Lymphoma remission, %[b]
Italy[13]	P	76	I	28 (12–63)	93.4
Italy[14]	P	7	I	42 (20–54)	100
Korea[15]	R	28	I	24 (2–74)	88.9
Germany[16]	P	120	I	75 (2–116)	80
Japan[17]	P	38	I	37 (6–132)	76.3
United States[18]	P	28	I–II	41 (18–70)	56.5
Korea[19]	P	90	I–II	45 (15–109)	100
France[20]	P	34	I–II	35 (10–47)	79
Germany[21]	P	90	I	44.6 (12–89)	66
Portugal[22]	P	17	I	12 (2–39)	100
Spain[23]	P	24	I	51 (20–112)	91
Italy[24]	R	13	I	24 (14–36)	92
United States[25]	P	65	I	22 (3–73)	63.8
Italy-Swiss[26]	R	45	I	22 (2–66)	68
Taiwan[27]	P	31	I	70 (20–85)	80
Austria[28]	R	22	I	25 (2–27)	68.2
Europe[29]	P	62	I	NA (1–48)	74.2
Japan[30]	P	74	I–II	47 (12–108)	94.2
Italy[31]	R	9	I	NA	100
The Netherlands[32]	R	23	I–II	37 (20–60)	455
Japan[33]	P	18	I	35 (9–85)	77.8
Korea[34]	P	99	I	41 (11–125)	84.8
The Netherlands[35]	R	35	I–II	NA	45.5
Japan[36]	P	21	I	10 (3–21)	95.2
Japan[37]	P	13	I–II	16 (3–32)	100
Japan[38]	P	10	I	NA (6–36)	90
Japan[39]	P	15	I	21 (6–49)	60
Germany[40]	R	196	I	27 (1–120)	75.6
Lebanon[41]	R	19	I–II	21 (6–40)	47
Japan[42]	P	33	I–II	NA (16–58)	90.9
Italy[43]	R	60	I–II	65 (7–156)	79.2
China[44]	P	21	I	18 (1–51)	61.9

P, prospective; R, retrospective.
[a]All *H pylori*–positive patients enrolled.
[b]Remission rate observed in the *H pylori* eradicated patients.