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Clinical features & treatment of early-stage gastric mucosa-associated lymphoid tissue lymphoma

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***Background & objectives*: Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a common marginal zone lymphoma. The stomach is the relatively common origin of the MALT lymphoma, now termed as extranodal marginal zone B-cell lymphoma. Gastric MALT lymphoma has good prognosis due to clinical response to treatment and favourable overall survival. In this study, clinical characteristics and treatment of patients of early gastric MALT lymphoma were retrospectively analysed.**

***Methods*: Seventy patients with stages I–II MALT-lymphoma treated from April 2003 to August 2015 were included. The most common symptoms were abdominal discomfort, nausea, vomiting and other digestive symptoms. *Helicobacter pylori* eradication was done in patients with proven *H. pylori* infection. Patients in whom *H. pylori* eradication therapy was not effective, alternative treatments options including chemotherapy, radiotherapy and surgery, were given.**

***Results*: Fifty two patients with *H. pylori* infection underwent anti-*H. pylori* therapy, the total effective rate of anti-*H. pylori* treatment was 92.3 per cent (48/52). Thirty two patients were given anti-tumour treatment, including chemotherapy, radiotherapy and surgery. The total effective rate was 90.6 per cent (29/32). The five-year overall survival rate and five-year progression-free survival rate were 93.4 and 84.2 per cent, respectively.**

***Interpretation & conclusions*: For patients with early gastric MALT lymphoma, anti-*H. pylori* treatment may be effective. Patients with poor results of anti-*H. pylori* treatment need to be treated with anti-tumour therapy.**

Key words Anti-tumour - early stage - eradication - gastric mucosa-associated lymphoid tissue lymphoma - *Helicobacter pylori*

Mucosa-associated lymphoid tissue (MALT) lymphoma is classified as an extranodal marginal zone lymphoma (MZL) according to the 2016 revision of the World Health Organization classification[1]. It is the most common MZL type, accounting for 5 to 8 per cent of all B-cell lymphomas[2]. MALT lymphoma is a low-grade malignant B-cell lymphoma and has an indolent clinical-biological behaviour pattern. Gastric MALT

lymphoma is the most common, accounting for 75 per cent of all MALT[3,4]. The common symptoms reported include weight loss, nausea, vomiting, abdominal fullness and indigestion[5]. Weakness, night sweats, jaundice, fever and dysphagia occur less frequently. *Helicobacter pylori* is closely related to the occurrence of gastric MALT lymphoma[6]. Many studies have shown that *H. pylori* eradication therapy can be used as a first-line treatment for early low-grade gastric MALT with proven *H. pylori* infection[7,8]. Gastric MALT lymphoma is considered to be an indolent lymphoma with an excellent prognosis due to good clinical response to treatment and favourable disease-free and overall survival (OS)[9]. This study was undertaken to retrospectively analyze 70 patients of early gastric MALT lymphoma to evaluate the efficiency of anti-*H. pylori* infection and the effect of anti-tumour therapy.

Material & Methods

Patients data in the Hematology department of Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, were retrospectively reviewed. A total of 106 consecutive patients were selected based on pathological diagnosis, and it was verified by two histopathologists. Immunohistochemical expression showed CD79a (+), CD20 (+), CD5 (-), CD10 (-), cyclinD1 (-) and BCL-2 (-). Generally, 6-10 biopsy specimens were collected with three times bites at a point on the bottom of a lesion, and into the submucosa. The size was about 0.3 to 0.5 cm. Histopathological sections were independently verified by two histopathologists. Seventy of the 106 patients, 36 were in the advanced stages, thus 70 patients with early gastric mucosa-associated lymphoma were included. These patients had complete follow up from March 2003 to February 2018.

Data collection: Patient baseline and clinical data, including age, sex, disease stage, laboratory tests [(*i*) blood routine; (*ii*) blood metabolic panel: liver and kidney function, LDH and β2 microglobulin; (*iii*) *H. pylori* detection: 13C/14C urea breath test and gastric mucosal histological examination; (*iv*) bone marrow biopsy] and imaging examination [ultrasound for superficial lymph nodes, computed tomography (CT) or positron emission tomography (PET)-CT for chest, abdomen] were collected. All patients gave written informed consent, and approval for the study was obtained from the Institutional Review Board.

Patient treatment: Anti-*H. pylori* therapy: (*i*) The triple therapy including proton pump inhibitors omeprazole 20 mg, clarithromycin 500 mg, amoxicillin 1 g or tinidazole 500 mg, was given twice daily over a period of 7-14 days, or on the basis of triple therapy, ampicillin and tinidazole were used for 7-14 days; (*ii*) If the above anti-*H. pylori* treatment was poor, a three-line treatment for 10 days was performed: proton pump inhibitor, bismuth salt, tetracycline and tinidazole.

Anti-tumour therapy: Anti-tumour treatment was given to those patients who failed to respond to anti-*H. pylori* therapy in six to 12 months.

(*i*) Chemotherapy: FC protocol (fludarabine 25 mg/m^2 day 1-3, cyclophosphamide 250 mg/m^2 d1-3) or CHOP protocol (cyclophosphamide 750 mg/m^2 d1, adriamycin 50 mg/m^2 d1, vincristine 1.4 mg/m^2 total <2 mg d1, prednisone 100 mg d1-5).

(*ii*) Radiotherapy: low-dose radiotherapy, with a total amount of 30 Gy.

(*iii*) Surgery: Surgical treatment was considered for complications (such as bleeding and perforation) caused by gastric MALT that could not be treated by endoscopy.

Efficacy evaluation: The efficacy was evaluated according to the International Working Group (IWG) standard[10]. After anti-*H. pylori* treatment for 4-6 wk, the efficacy was evaluated. The biopsy tissue of the gastric antrum and the gastric body ≥10 pieces were taken by gastroscope for detection. Patients with complete remission (CR) were evaluated for anti-*H. pylori* efficacy every six months. For patients who have not reached CR for six to 12 months, endoscopic biopsy was performed on the lesion again to know whether it was transformed into diffuse large B-cell lymphoma, and anti-tumour therapy was needed.

Statistical analysis: All data were analyzed using the SPSS version 18.0 software (SPSS, Chicago, IL, United States). The survival curves were constructed by the log-rank test method. OS was defined as the interval from the diagnosis of relapse/refractory gastric MALT to death or the end of follow up. Progression-free survival (PFS) was defined as from the diagnosis of relapse/refractory gastric MALT to progression disease (PD), death or the end of follow up (The PFS for this study was from March 2003 to February 2018).

Results

Of the 70 patients, 32 were males (45.7%) Forty one patients were in stage I and 29 in stage II. The

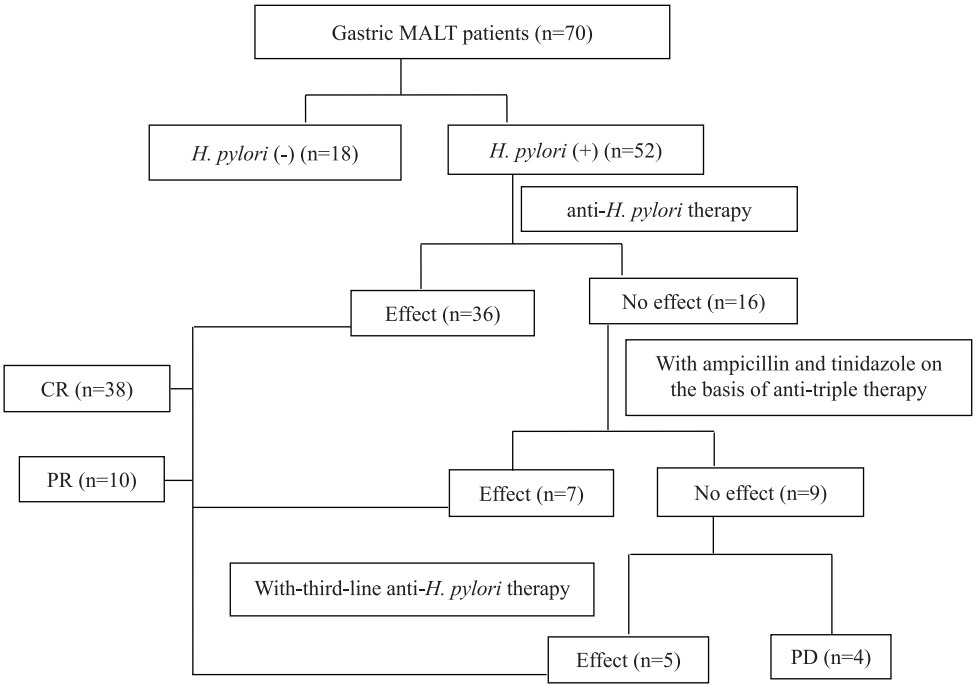

Fig. 1. Flow diagram showing of anti-*Helicobacter pylori* treatment in patients with gastric mucosa associated lymphoid tissue (MALT) lymphoma. CR, complete remission; PR, partial remission.

age ranged from 18 to 63 yr with the median of 54 years. Inclusion criteria: (*i*) MALT confirmed by pathology and, (*ii*) early gastric MALT determined by Musshoff staging system[11]. Clinical manifestations were abdominal discomfort, nausea, vomiting and other digestive symptoms. There were 12 patients with B symptoms (fever, night sweats, weight loss). Bone marrow was not involved in any of the patients. Anaemia was shown in five, lactate dehydrogenase (LDH) was increased in nine and β2-microglobulin was increased in seven patients. *H. pylori* infection rate was 74.3 per cent (52/70).

Treatment outcome and short-term effect: Effect of anti-*H. pylori* therapy: Fifty two patients with *H. pylori* infection underwent anti-*H. pylori* therapy. The therapy was effective in 36 patients. The remaining 16 patients with ineffective anti-*H. pylori* infection continued to be treated with ampicillin and tinidazole for 7-14 days on the basis of anti-triple therapy. The treatment was effective in seven and for the remaining nine patients with *H. pylori* infection, five were treated with third-line anti-*H. pylori* therapy and four patients were scheduled for anti-tumour therapy due to PD. The total effective rate of anti-*H. pylori* treatment was 92.3 per cent (48/52). Of these 48 patients who were effective in anti-*H. pylori* treatment were evaluated, 38 achieved CR and 10 patients were on PR, These 10 patients with partial remission were treated with anti-tumour therapy (Fig. 1 and Table).

Effect of anti-tumour treatment: Eighteen *H. pylori*-negative patients, four patients of disease progression and 10 with anti-*H. pylori* therapy but not in CR, were treated with chemotherapy. After chemotherapy, 21 of 32 patients achieved CR, and the total effective rate was 65.6 per cent. Of the remaining 11 patients with PR, three underwent surgery and achieved CR, the other eight patients adopted radiotherapy, five achieved CR and three had PD. The total effective rate was 90.6 per cent (29/32) after anti-tumour therapy (Table).

Survival outcome: Seventy patients were followed up until August 2018, five patients were lost to follow up. The percentage of loss to follow up was 7.14 per cent. The median follow up months were 30 (20-60). Seven patients died. One patient died of myocardial infarction and the rest died of recurrence and progression of the disease. The five-year OS rate and five-year PFS rate in 65 patients (excluded five patients who were lost to follow up) were 93.4 and 84.2 per cent, respectively (Fig. 2).

Discussion

Most of the patients with gastric MALT are adults, with the median age of 60 yr, and the incidence of

Table. Types of treatment given to 52 patients positive for *Helicobacter pylori*

Anti-hpylori treatment	Anti-tumour treatment (n)	Chemotherapy (n)	Operation (n)	Radiotherapy (n)
CR	38	21	3	5
PR	10	11	0	0
PD	4	0	0	3
Total	52	32	3	8

CR, complete remission; PR, partial response; PD, progressive disease

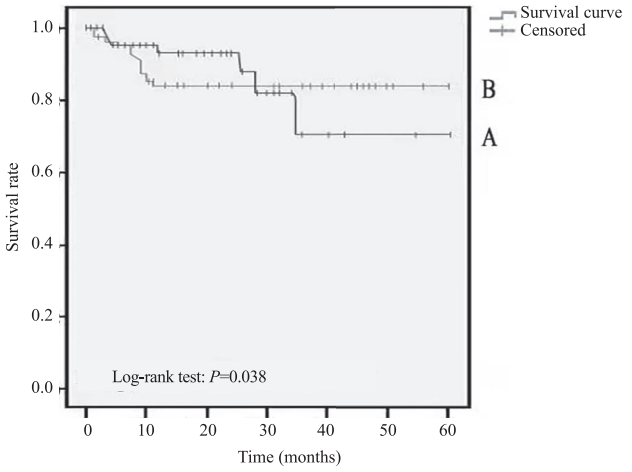

Fig. 2. The five-year overall survival (A) and progression-free survival (B) of the 70 patients.

gastric MALT in woman is slightly more than in man[12]. Many studies have confirmed the correlation between *H. pylori* and gastric MALT[13,14]. *H. pylori* infection may cause cell immune response and lead to the release of a series of cytokines, thereby activating the inflammatory response and causing epithelial cell damage through autoimmunity[15]. Hussel[16] *in vitro* experiments showed that the gastric lymphoid cells derived from the poorly differentiated B-cells proliferated under the stimulation of *H. pylori* and the hyperplasia reaction must have the presence of non-tumour-like T lymphocytes. If the T-cells were removed from the culture medium, the proliferation of gastric mucosal related lymphocytes would be terminated[17]. *H. pylori* can induce neutrophils to release oxygen free radicals, cause gene abnormalities and promote B cell degeneration to form abnormal clonal hyperplasia and B-derived lymphoma[18]. In this study of 70 patients with early gastric MALT, 52 patients (74.3%) were infected with *H. pylori*. These patients were treated with anti-*H. pylori* therapy, 38 patients achieved CR and 10 achieved PR. In a previous report the *H. pylori* infection rate was found to be 80.3 per cent[19]. The difference in *H. pylori* infection rate may be related to sample size, region, and race. Our findings confirmed the importance of eradication of *H. pylori* in the treatment of gastric MALT was further confirmed, indicating that anti-*H. pylori* therapy may be used as a first-line treatment for early gastric MALT. Anti-tumour therapy was given to 32 patients, of them, 29 had CR, the total effective rate was 90.6 per cent. Therefore, anti-tumour therapy may be used as an alternative after the failure of anti-*H. pylori* treatment. Since the study was conducted in patients with early gastric MALT lymphoma, the five-year OS rate was high, reaching 93.4 per cent.

Most of the cases are *H. pylori* associated and therefore eradication therapy should be considered as first line treatment in patient with localized disease. The absence of *H. pylori* on multiple biopsies supports the hypothesis that *H. pylori* may be present in early lymphoma stages, but may disappear with tumour progression[20]. *H. pylori* negative cases often present in a more advanced stage and require more aggressive treatment[21].

In summary, we retrospectively analyzed the clinical characteristics, diagnosis, treatment and survival of 70 patients with gastric MALT lymphoma. There were several limitations in this study. The therapeutic effects of patients undergoing surgery, chemotherapy and radiotherapy were not compared. By comparison, more effective treatments could have been found. In addition, the sample size in this study was small. Subsequent studies need to be done with a large sample to confirm the present findings.

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***Conflicts of Interest*:** None.

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