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SM Journal of Gastroenterology & Hepatology

Review Article

Primary Gastric Lymphoma

Ming-Chih Chang[1]* and Sung-Hsin Kuo[2]*

[1]*Department of Hematology/Oncology, Mackay Medical college Hospital, Taiwan*
[2]*Department of Medical Oncology, Taiwan University Hospital, Taiwan*

Article Information

Received date: Feb 14, 2017
Accepted date: Apr 17, 2017
Published date: Apr 28, 2017

***Corresponding author**

Ming-Chih Chang, Hematology/Oncology, Mackay Medical college Hospital, Taiwan, Tel: +886 2 2636 0303; Email: mmhdonald@yahoo.com.tw

Keywords Gastric lymphoma; MALT; H pyroli eradication; Surgery; Chemotherapy; Rituximab

Abstract

The treatment of primary gastric lymphoma is evolving in post-rituximab era. The role of *Helicobacter pyroli* eradication alone can cure not only Mucosa-Associated Lymphoepithelial Tumor (MALT) but also some of diffuse large B cell lymphoma with or without MALT component. The efficacy of rituximab containing chemotherapy is so effective that the role of surgery is overshadowed. There are many studies, although most of them were retrospective trials, however it highlights the current mainstay of immune-chemotherapy provided an outstanding long term survival more than 80-90%.H pylori In real world there are substantial patients may receive surgery first, yet still needs post-operative adjuvant chemotherapy for some of them has a risk of relapse of lymphoma. And recent studies showed there's no statistical difference between the two modalities. The main reason for patients proceeded to surgery as primary treatment is the gastroenterologist preference and showed no difference in terms of progression free survival and overall survival. The rituximab was introduced to lymphoma treatment since 1999, and demonstrated a superior long term survival in diffuse large B cell lymphoma for R-CHOP relatively to CHOP regimen. The highly effective treatment made PGL being easily curable disease; furthermore there are new insights of why and how the antibiotic therapy as exclusive treatment for limited disease will be a mainstay in treating this malignancy. We make a proposal how to treat the primary gastric lymphoma and MALT, and highlight the changing treatment modalities with regards to the integration of *Helicobacter pyroli* eradication to conventional chemotherapy as well as the complimentary role of surgery and radiotherapy.

Introduction

Primary Gastric Lymphoma (PGL) is not a common cancer and account for 10% of malignant lymphoma and approximately 2-8% of gastric cancer [1]. The correlation with *Helicobacter pylori (H. pylori)* infection with MALT is now well documented and some of the low grade MALT can be cured sorely by triple agent eradication therapy. The most common type of PGL is diffuse large B cell lymphoma followed by MALT. In the recent 15 years chemotherapy combined with anti-CD 20 monoclonal antibody such as rituximab, achieved higher complete response rate and more than 80% are long-term survival. The so-called R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristin, prednisolone) now become the new gold standard therapy [2,3]. The role of surgical resection prior to chemotherapy is not commonly applied in the real world, as yet the diagnosis can be made by endoscopic biopsy. *H pylori* There is approximately 10-20% cases of suboptimal response (no complete remission up to 4 cycles) to R-CHOP or patient is non-fit to tolerate the immuno-chemotherapy will be feasible to surgical resection as a salvage or alternative therapy. The radiotherapy as an adjuvant therapy is currently less commonly considered as primary treatment but still a good option for advanced disease and the elderly who are non-fit to aggressive chemotherapy. Patients with advanced PGL with high international prognostic index risk and along with co-morbidity diseases are prone to get treatment related complications from above-mentioned modality of treatment. The treatment paradigm is changing since our understanding to the pathogenesis of MALT and diffuse large B cell lymphoma.

With great improvement of modern chemotherapy and supportive care, consequently a global therapeutic approach to the cure of PGL has completely changed over the last one decade: innovative, conservative options to reduce treatment toxicity, thus preventing systemic relapses, have made their appearance and are on the rise. Among the gastric malignancies PGL has the most favorable outcome not only in localized disease but also in stage IIb/IV disease. It is highly sensitive to chemotherapy and anti-CD 20 immunotherapy [1-3]. The primary role of surgery or chemotherapy as the mainstay is an issue of debate [4]. However, there is, as yet, no randomized control trial to define the primary treatment of PGL, either surgery or chemotherapy or combined modality. Is it now clearer that *H pylori* eradication alone has the possibility to cure the gastric MALT. Nevertheless, there's more and more clinical evidence that some portion of both MALT and DLBCL can achieve long term survival by eradication of *H pylori* without chemotherapy. And use chemotherapy is justified afterward for partial tumor regression or till disease progression or patients who have t(11;18) chromosomal aberration.

Pathogenesis of Gastric Lymphoma and MALT

Issacson et al proposed a theory that the early MALT caused by chronic inflammation triggered by infection or autoimmune disorders, including *H. pylori* gastritis, Sjogren syndrome [5]. It causes

abnormal B cell proliferation and T cell infiltration and accumulation of MALT from which the gastric MALT lymphoma arises. In histology all of the PGL originated from B lymphocyte, the normal counterpart is germinal center B cell. The causes of PGL is partly from de novo DLBCL, and partly transformed from low to high grade MALT and lastly diffuse large B cell lymphoma (DLBCL). The cytokine changes and genetic aberration give this pathogenesis. It is well known that *H. pylori* play a role in peptic ulcer disease, gastric adenocarcinoma as well as gastric lymphoma and MALT. It can be argued what the cause of same pathogen and yielded different outcome. It was shown that *H pylori* has different strains with varied virulence, the prevalence of CagA strains expression is higher in DLBCL than in MALT [6,7]. There are several chromosomal alterations especially 3,12,and 18 are involved. Among them two recurrent chromosomal changes in this tumor were identified-the t(11;18) (q21;q21) and the t(1;14) (p2;q32). The t(11;18) produce the fusion of AIP2 at 11q21 which encode of inhibitor of apoptosis protein IAP to a gene at 18q21 named MLT1. The different strains virulence occurred in different vulnerable host might emerge variable B cell and T cell immune repertoire, and produce gastric lymphocytes infiltrates. The segment of MLT1 and FOXP1 bind to BCL10, this fusion protein strongly activate NF-kB, in turn suppress host cell apoptotic response to viral or microorganism infection.8H pylori All of the genetic alteration appear to lead to deregulation of the pathway. Once the fusion gene developed the gastric MALT become *H. pylori* independent growth and no longer regress by antibiotics eradication.

Histological Classification of PGL

Primary malignant lymphoma of the stomach are almost all non-Hodgkin's type and of B-cell lineage. These lymphomas usually arise from MALT, also known as extranodal marginal zone B-cell lymphoma by 2008 WHO classification (Low and High grade), and the old term was also called pseudolymphomas or IPSID (immunoproliferative small intestinal disease). Diffuse large B-cell lymphoma is the most common, account for 50-55% or with MALT component and large cell transformation, followed by MALT around 40%. Other types including mantle cell lymphoma (malignant lymphomatous polyposis), follicular lymphoma, Burkitt 's or T-cell lymphoma are quite rare, often involving intestinal tract as well and may not be sole gastric lesion. The diagnosis is made on the morphological features. Lymphoma should not be diagnosed on the basis of clonality studies by immunehistochemistry or molecular techniques alone. It commonly located in the gastric antrum. The most common type is ulcerative lesion [9]. It may be polypoid and fungating like lesion mimicking gastric carcinoma. In low grade cases, multiple erosions or superficial ulceration may be present. Lymphoepithelial lesions defined as glandular structures expanded and destroyed by groups of more than 3 lymphoid cells. Immunostaining for CD20, CD79 and cytokeratin are useful for demonstrating lymphoepithelial lesions. CD5, CD10, CD23 or cyclin D1 are negative [5,8-10]. Occasional non destructive lymphoepithelial lesions alone are not sufficient to diagnose lymphoma. Carefully look for compact clusters, confluent aggregates or sheets of blast cells that makes the tumor high grade. The high grade MALT is characterized by destructive infiltrate of clusters or sheets of blast cells with few or no lymphoepithelial lesions. Mitoses and apoptotic bodies were frequently seen. It may be difficult in distinguishing from diffuse carcinoma, sarcoma, or even T-cell lymphoma or metastatic melanoma [10]. The epithelial lesions infiltrated by melanoma cells may mimic lymphoepithelial lesions. Mucin stains and immunostaining for cytokeratin, CEA, common leukocyte antigen, B and T cell markers are very helpful.

Sign and Symptom of PGL

The most common symptom at presentation is abdominal pain account for 80% followed by melena 36%, nausea, vomiting, hematemesis and ileus. B-symptoms as fever, body weight loss are common, and some bulky disease. Most of PGL located at antrum (50%) followed by corpus (body 24%) and fundus [11]. One third patients can be characterized as a benign disease from gastrocopic point of view. The endoscopic pattern of MALT/DLBCL may be nonspecific even under the narrow band image. It is prudent to perform a biopsy if with clinical suspicion. The median age is around 50 to 55 years, male to female ratio 1.2:1. Increase LDH serum level is common, even for localized lymphoma [11]. The ratio of GCB (germinal center B cell, less aggressive) to non-GCB phenotypes was about 1:1.85. Pure MALT lymphoma accounted for 20-40% varied from series [8,9,11,12].

Staging of PGL

All patients are evaluated by abdominal / chest CT scan and endoscopy or endoscopic ultrasound, bone marrow biopsy, PET scan, LDH, beta-2 microglobulin and access the international prognostic score IPSS. Classification of the tumor stage was according to the Musshoff's modification of the Ann Arber staging system [13]. Stage IE denotes tumor remains confined within the stomach; stage IIE-1, which has peri-gastric nodal involvement only, and stage IIE-2, which has more distant nodal involvement below the diaphragm. Stage IIIE denotes nodal involvement above and below the diaphragm, and stage IV denotes multiple visceral organ involvement. Lugano staging system was also applied as well and it omit the stage III disease [14].

Management of pgl: How We Use the Different Modalities Fit or Non-Fit?

Role of surgery

Traditionally the gastric lymphoma was managed by surgeon with partial or total gastrectomy not only for diagnosis, but staging and for cure purpose. Yet there were some 20% patients relapsed and adjuvant chemotherapy after surgery was considered. Indeed, from a thorough review of the literature, most of the relevant literature pertaining to this surgery has related to studies featuring, generally small numbers of patients as well as such studies having been conducted retrospectively and during the 1980s and the 1990s. Thus, many investigators still advocated surgical resection in order to debulk the lesion mass and to accurately stage the lesion to attempt to prevent post-surgical perforation [15-18]. During the early 1990s, some authors had suggested that chemotherapy alone was effective for the sole treatment modality and may also have been effectively prevent the morbidity from gastrectomy, such approach supporting gastric preservation for subsequent residual diseases [19-22]. Further, yet other authors have recommended surgery as being able to achieve a cure for primary gastric lymphoma, particularly for stage IE disease [23-25]. Those researchers who suggested surgery either with or without associated chemotherapy focused on the accurate staging of the tumor, less hemorrhage or perforation of the stomach during the treatment. Then the development of endoscopic

ultrasound made laparotomy biopsy become unwarranted and help to assess the risk of treatment related hemorrhage [23]. Meanwhile, most of the reports have revealed a rather low incidence of severe hemorrhage or perforation, accounting for, respectively, 2.1% and 1.7% of those individuals treated with chemotherapy without surgery and, respectively, 2.2% and 0.9% of those individuals treated only surgically [26,27]. Such evidence does not enhance the role of surgery and it became less important than previously considered. In recent real world practice we change the algorithm toward non-surgical modality, and the controversies will be clarified.

The controversies of primary treatment of PGL should be individualized to patient fitness.

The issue of optimal treatment for localized PGL has not been resolved. In the 1980s, gastrectomy, because of its low surgery-related mortality (2–5%), was used to treat PGL [23-26]. According to results from the Mayo Clinic, the 5-year-survival rate was reported to reach 75% with curative resection, and 32% with palliative resection [17]. For stage IE PGL, the cure rate could be even as high as 80%. However, the success of surgical management of PGL depends on the size of tumor, the depth of tumor penetration into gastric tissue, and the involvement of regional lymph nodes [23]. Some investigators began using chemotherapy, mostly CHOP [15,17,26] and R-CHOP after year 2000 [1-3], to control the tumors and to prevent postoperative morbidity. A study by Maor et al showed that the six-year overall survival of patients treated with chemotherapy alone was 76% [17]. The recent publications gave even better results with 5-year OS over 90% [1,2]. H pylori However, for bulky tumors, the advantage of chemotherapy is offset by the potential tumor bleeding and gastric perforation [4]. In 1999 there was a publication of international survey to investigate the treatment consenus [27]. It reviewed the management of gastric lymphoma, formatted questionnaires were mailed to leading institutes with a special interest in this field in 19 centers of Europe, the United States and Japan. Gastroenterologists are far more inclined to perform a (partial) gastric resection (with or without additional radiation therapy or chemotherapy) than haematologists and medical oncologists. And some European center as well as USA preferred to use radiotherapy as adjuvant or salvage therapy [27,28]. Therefore, some investigators suggested that debulking surgery followed by chemotherapy and/or radiotherapy, so-called combined modality, achieved better clinical outcome mainly better tumor control with reduced complication rates [29-34]. In our series, all five patients who developed gastric perforation were in the chemotherapy-alone group, and eventually died of this complication. In contrast, none of the patients receiving the combination therapy had this complication, suggesting an important role for surgery in selected patients [4]. Of note, five patients of major complication, four in the chemotherapy-alone group and one in the combination therapy group, developed gastro-intestinal bleeding at the time of disease progression. The overall surgical morbidity and mortality were 15.4% (2/13) and 7.7% (1/13), respectively, similar to what has been reported by Rackner et al [35]. The rate of surgical complications might counteract against the benefit from tumor control. This notion is further supported by the results of Salles et al, showing that for localized PGL, surgical resection prior to chemotherapy did not affect the complete response rate, survival rate, or the disease-free survival [15]. Similar results have also been demonstrated in several studies on Asian patients and in the Grouped'Etude des Lymphomes Digestifs (GELD) and Grouped 'Etude des Lymphomes de l'Adulte (GELA) studies [37-42]. Such evidence suggests the role of surgery in the primary treatment of PGL is declined.

Although surgery for PGL appears to have a less priority role in recent studies, it might enhance the effects of immune-chemotherapy in stage IE PGL [41,42]. Patients treated with stomach-preserved surgery followed by three cycles of chemotherapy had a better five-year survival rate than patients treated with chemotherapy alone [29,32-34]. We also noticed an improved outcome in patients who received treatment after year 2000, probably due to better supportive care and a more widespread use of G-CSF for febrile neutropenia. A subgroup of patients was identified who might be more likely to develop chemotherapy-induced life-threatening complications. Often treated in an outpatient setting, these patients failed to achieve a complete response to chemotherapy. To avoid such severe complications, we recommend re-evaluating patients by endoscopy after two cycles of chemotherapy. At the same time, patients should be warned that complications such as gastric perforation and bleeding, although not common, are possible and be made more aware through comprehensive education.

In real world practice, it would appear that the gastroenterologist's point of view would be crucial as regards the making of a decision in algorithmic approach, in which whether to refer patients to a medical oncologist or a surgeon [27]. Although chemotherapy alone is very effective in terms of complete response rate and 5 year disease free survival and overall survival comparable to surgery plus adjuvant chemotherapy [1-4]. Yet, not all the gastroenterologist follow this recommendation, and used to referring patients to medical oncologist and surgeon at the same time; more or less they prevail the surgery role and also notice the importance of chemotherapy to circumvent distant metastasis.

In one report from China, a 200 cases of PGL, 24 cases received chemotherapy alone, 29 cases surgery alone, 132 cases underwent surgery plus chemotherapy, and 15 were of palliation [41]. The ten-year survival rates were 55.0%. Another study identified 79 patients 30 patients (38%) underwent surgery, 74 (92%) received chemotherapy, and 18 (23%) received radiotherapy. The five-year OS and DFS rates were 91.2% and 83.9%, respectively, in patients with stage I/II or IIE disease and 70.6% and 65.5%, respectively. Treatment modality (surgical or conservative) had no impact on OS or DFS in early stages.

The Role of Rituximab Containing Chemotherapy

The safety of chemotherapy is improving with modern supportive care, giving more survival benefit. The emergence of anti-CD 20 monoclonal antibody such as Rituximab proved to be very effective in treating B-cell lymphoma. The GELA study showed a 15% ten-yr disease free survival benefit, comparing R-CHOP with CHOP, in over all diffuse large B cell lymphoma, but no data specialized for PGL [43]. The PGL treatment make a new paradigm, R-CHOP is a front line treatment of choice. We will recommend CHOP-21 for four to six cycles, rather than traditional 8 cycles, and keep rituximab for 8 cycles.

One study from Japan evaluates clinical outcomes of PGL in the rituximab era; they conducted a retrospective, multicenter analysis of 95 patients with PGL. In 58 patients with localized disease, 3-year progression-free survival (PFS) and overall survival (OS) were

91% and 91% for patients with six cycles of rituximab plus CHOP (R-CHOP) and 92% and 95% for patients with three to four cycles of R-CHOP plus radiotherapy (Log-rank test, P = 0.595 and P = 0.278, respectively). No patient underwent surgery [1]. Clinical outcomes of PGL were extremely favorable and promising for localized-stage patients in the rituximab era [3]. Also recent report of Chinese patients who received chemotherapy with rituximab (at least 3 cycles) had a mean OS of 72 months (95% CI 62-81) versus 62 months (95% CI 47-76) for patients chemotherapy alone(P = 0.021). This study reflected the additive benefit of rituximab when combined with chemotherapy [44]. However, a phase II clinical trial showed that the addition of rituximab to standard chemotherapy did not improve the outcome in early-stage PGL due to high long-term survival in both groups [2].

The Issues of Treatment Related Complications

In those patients who achieved the complete response, the very late relapse of gastric lymphoma is quite rare and still can be re-treated with same chemotherapy or salvage chemotherapy. The toxicity and safety for R-CHOP is an important issue. Some patients is rather fragile especially for the elderly, the drawback of R-CHOP regimen will give 10-20% grade III/IV febrile neutropenia. The infection rate increase in dose-density regimen. The most troublesome side effects of R-CHOP are pulmonary infection such as PJP pneumonia, pulmonary interstitial disease, cardiovascular event, congestive heart failure, and reactivation of hepatitis B in East Asia countries. The fulminant hepatitis account for 10-16% in hepatic B antigen positive carrier without anti-viral prophylaxis, and some of them succumb to hepatic failure. The hepatitis B seroconversion from anti-HBc to HBsAg positive rate is around 6-8%, and very low death rate, partly due to early recognition and low HBV-DNA viral load. We recommend early anti-viral prophylaxis by using tenofovir or entercavir even though the liver function is normal. And it is judicious to follow-up the HBV DNA viral load. This prophylaxis should be used for 12 months or 6 months after completion of chemotherapy. The interstitial lung fibrosis and anthraxcycline or rituximab related cardiomyopathy is another important issue, which needs high clinical alert and pay much attention to patients with pre-existing co-morbidity. R-CVP or rituximab plus bendamustine will be an alternative regimen for fragile patients for who cannot tolerates R-CHOP or alike regimen.

The Rationale of Treatment Modalities: Keep Open-Minded Approach

In our own series, we refer patients to surgeon for subtotal gastrectomy for those with large tumor and high co-morbidity, and preserve radiation therapy for those who are not feasible for operation whatsoever. And add two to four cycle of post-operative salvage chemotherapy as consolidation purpose. Subtotal gastrectomy is justified in selected cases. Surgery is indicated to treat complications such as gastric perforation, uncontrolled hemorrhage. A small portion of patients may encounter small amount melena passage, most often one week after chemotherapy, due to tumor necrosis, which happened during first two cycles. It is always a transient less severe event and resolves with supportive care over time.

In real world practice, the gastroenterologists identify patients with PGL and refer to medical oncologists for staging procedure, risk stratification. And chemotherapy is the primary treatment given to patients without surgery. For those centers where surgery is the standard primary treatment, subtotal gastrectomy replaces total gastrectomy, yet adjuvant chemotherapy should be done for those patients with positive surgical margin, large tumor (>5cm) and lymph nodes involvement. We also consider surgery alone will be sufficient to cure PGL in low risk, stage IE disease, and it will be a good alternative primary treatment for those patients who are fragile and prone to develop R-CHOP related afore-mentioned complications. For those patients who have MALT/DLBCL or DLBCL with MALT component and positive HP infection, we may choose to give HPE first before chemotherapy, some of them can be cured without chemotherapy. If not, the algorithm shown in figure 1. will suggest to proceed to immune-chemotherapy.

Advanced PGL

Advanced PGL is still a challenging issue and the improvement of modern treatment is not always satisfactory. A series of 37 patients with advanced disease, 3-year PFS and 3-year OS were 43% and 64% for patients with R-CHOP chemotherapy with or without radiotherapy; [1] the prognosis is still poor for advanced-stage patients even in the rituximab era. In our series, the overall survival was significantly lower for advanced PGL patients than localized PGL patients and 20% of advanced disease could not achieve complete remission including death, signifying again that stage is an important prognostic factor in the treatment of PGL [4]. In the chemotherapy alone group, three out of seven complete responders of advanced PGL patients (3/19 or 15.8%) were long-term survivors (DFS more than 6 years), while all four patients in the combined-modality group died. The outcome of combined-modality group is dismal due to higher incidence of treatment related tumor bleeding as well as febrile neutropenia, the incidence was 75.0% and 50% respectively, than chemotherapy alone group, 31.6% and 15.8%, respectively. The role of surgery is limited in the treatment of advanced PGL in our series and other [4,45]. The new chemotherapy agents and next generation monoclonal antibody or combination with lenalidomide, a strong immune modulator for non-germinal center type lymphoma, may provide a better response for those who are difficult to treat.

How I Treatment of MALT Lymphoma

The MALT lymphoma account for 25-40% all gastric lymphoma, it can be classified as low grade MALT, high grade MALT and transformed from high grade to DLBCL. The low grade MALT is very indolent and always almost localized disease. Patients shall receive a triple therapy with omeprazole (20 mg twice a day) or other proton pump inhibitors, amoxicillin (1 g twice a day) and clarithromycin (500 mg twice a day) for 14 days, followed by omeprazole for other 21 days. One report of 61 patients with primary gastric large B-cell lymphomas were treated with anti HP treatment and 42 of them showed a complete response [46]. The median time to complete response was 9.6 months for MALT with high grade predominant and 5.5 months for low grade MALT in the early year 2010 and the new modified HP eradication achieve even earlier time to response. The longer period of follow-up was reported in this study showed all the 14 MALT patients with CR remained relapse-free after a median follow-up of 63 months [49]. Histological regression of the lymphoma was complete in 19/44 patients (43%). No regression was noted in the 10 *H pylori* negative patients. Among the 34 *H pylori* positive patients, the *H pylori* eradication rate was 100%; complete

regression rate of the lymphoma increased from 56% (19/34) to 79% (19/24) when there was no nodal involvement at endoscopic ultrasonography [50]. There was a significant difference between the response of the lymphoma restricted to the mucosa and other more deep seated lesions ($p<0.006$). However, using multivariate analysis, the only predictive factor of regression was the absence of nodal involvement ($p<0.0001$) [51].

The high grade MALT can be either treated with anti-*H pylori* regimen alone or combined with short course of CHOP or R-CHOP. Some authors advocate anti-*H pylori* regimen alone will be sufficient to cure the disease, however we may overlooked the potential sampling error that some part of MALT is undergoing transformation to DLBCL, which is already become autonomy and independent from MALT1 gene control. In our clinical observation there is a part of high grade MALT is not cured by anti-*H pyroli* regimen alone and turned to be wide-disseminated MALT disease. The risk factors will be MALT infiltration to muscularis mucosa, nodal involvement and presence of t(11;18)(q21;21). It needs not to be transformed as DLBC before dissemination, and keeps the original morphology as extranodal marginal zone lymphoma. It is not uncommon to see patients histology presented with composite high grade MALT and DLBCL in same specimen. We do not routinely used chemotherapy for high grade MALT (now called MALT/DLBCL), but staging procedure should be done as an indolent or aggressive lymphoma. The stage III/IV disease should be treated as advanced indolent lymphoma accordingly. The MALT can be disseminated or present at an advanced stage or involved other extranodal sites as approximately one third of cases [47]. For those patients of high grade MALT with transformation (the old term) and composite with DLBCL, it was revised in WHO 2008 classification, the recommendation will be anti-*H pylori* regimen followed by four cycles with CHOP or R-CHOP; whereas anti-*H pylori* regimen followed by four to six cycles of rituximab remained for the elderly and fragility. However, This approach now modified as HPE alone without chemotherapy will be sufficient if patient achieve complete remission, the endoscope will define the response as GELA scoring system [46,48].

Revisit of MALT/DLBCL and why the role of antibiotics treatment for primary gastric lymphoma with and without histologic evidence of MALT is important? Can some primary gastric lymphoma be cured by antibiotics and PPI alone? H pylori And what will be the most appropriate algorithmic approach? Some investigators consider the future treatment of PGL will be chemotherapy free and surgery free. Previous studies have reported that a substantial proportion of patients with H. pylori-positive early-stage gastric high-grade MALT lymphoma achieved complete remission (CR) through first-line anti-*H pylori* regimen. Furthermore, 4 prospective studies and one retrospective study reported that some early-stage H. pylori-positive gastric high-grade MALT lymphoma patients can also achieve long-term CR after first-line anti-*H pylori* regimen [47,48-55]. Most of these patients were treated with antibiotics plus proton pump inhibitors for 2 weeks, and had multiple sequential follow-up endoscopic examinations to monitor disease progression or verify CR. From aforementioned results, the CR rate was achieved in 33 (58.9%) of 56 patients with stage IE-IIE1 gastric high-grade MALT lymphoma [47,48,53-55]. The median time to CR after completion of HPE was 4.0 months (95% confidence interval: 2.1-5.9), and all patients who achieved CR remained lymphoma-free after a long-term follow-up [47,48,53-56]. Considering that the distinction between diffuse large B-cell lymphoma (DLBCL) components and their origins is not as straightforward as with similar MALT lymphoma components in gastric high-grade MALT lymphoma, [57,58] the term "high-grade MALT Lymphoma" is no longer considered appropriate. In 2008, the WHO lymphoma classification recommended that gastric lymphoma cases that show transformation into large-cell lymphomas should be classified as DLBCLs with MALT (DLBCL(MALT)) instead of high-grade MALT lymphomas [10, 59,60].

In contrast to DLBCL (MALT), gastric DLBCL without histologic evidence of MALT (gastric "pure" DLBCL) is generally thought to originate de novo and is therefore considered unrelated to *H pylori* infection. However, previous studies have displayed that gastric "pure" DLBCL may be epidemiologically associated with HP infection [61]. Several anecdotal case reports also revealed that early-stage gastric "pure" DLBCL may be dependent on H. pylori, and eradicating *H pylori* by antibiotics can cure these cases [55]. In a Japanese retrospective study, Tari et al reported that 4 (26.7%) of 15 patients with stage IE H. pylori-positive gastric "pure" DLBCL achieved CR following first-line anti-*H pylori* regimen, with a median interval to CR of 3 months, and all patients who achieved CR had tumor invasion of the mucosa or shallow lesions of the submucosa [62]. In the Taiwan explorative study evaluating the efficacy of first-line anti- *H pylori* regimen on early-stage (stage IE/IIE1) H. pylori-positive gastric "pure" DLBCL and DLBCL (MALT), Kuo et al reported that 68.8% (11/16) of "pure" DLBCL patients achieved CR. In their study, patients received their first upper-gastrointestinal endoscopic follow-up examination between 4 and 6 weeks after completing antibiotic therapy [63]. The median interval from completion of first-line anti-*H pylori* regimen to CR was 2.1 months. Eleven patients achieved CR after antibiotics, and were free of lymphoma at a median follow-up of 3.9 years, except one patient who died of lung cancer [65]. Furthermore, Ferreri et al revealed that in a multicenter phase II study (HG-L1 trial), 6 (55%) of 11 gastric "pure" DLBCL patients achieved CR following antibiotics, with a long-term remission [66]. The CR rate was achieved in 21 (50%) of 42 patients (with a remission rate from 26.7% to 68.8%). Overall, these findings indicate that a substantial number of H. pylori-positive gastric "pure" DLBCLs remain responsive to first-line *H pylori* regimen therapy [67]. However, large-scale prospective studies are required to validate its use as first-line antibiotics for treating early-stage H. pylori-positive gastric "pure" DLBCLs.

Because gastric DLBCL tumors, including "pure" DLBCL and DLBCL (MALT), can grow rapidly, patients who do not show signs of remission at the first endoscopic follow-up examination should be immediately referred for conventional chemotherapy or other modality therapy [63]. In the aforementioned results of Kuo's study and HG-l1 trial, patients whose tumor can't respond to first-line *H pylori* regimen can be effectively salvaged and was achieved CR with immunochemotherapy, chemotherapy, or radiotherapy [62,64]. Taken together, these studies demonstrate that patients with stage IE1/ IIE1 *H pylori* -positive gastric DLBCL can be safely managed with antibiotics alone. Importantly, patients unresponsive to antibiotics can be safely salvaged with conventional immunochemotherapy.

Chen et al. conducted a prospective study from Taiwan Cooperative Oncology Group, a first-line anti-*H pylori* regimen in the treatment DLBCL (MALT) and MALT lymphoma of the stomach. He reported that the CR rate of tumors limited to the

mucosa or submucosa and that of tumors in the muscularis propria or beyond was 80% (8/10) and 29.4% (5/17), respectively (P = .018), whereas a similar Japanese study reported 66.7% (4/6) and 25% (1/4), respectively (P = .524) [49]. A recent analysis of 1215 MALT lymphoma and 56 DLBCL(MALT) patients showed that the tumor regression rate following successful HPE was higher in MALT lymphoma patients than in DLBCL(MALT) patients (78.5% vs 62%; P = .0062) [65]. Those patients with gastric "pure' DLBCL who received first-line anti-*H pylori* regimen without chemotherapy, Kuo et al. showed that the CR rate of pure DLBCL limited to mucosa and submucosa and extended into the muscularis propria or beyond was 100% (5/5) and 54.5% (6/11), respectively (P = 0.119, Fisher exact test) [65]. Ferreri et al. also reported that among 6 patients whose tumors had invaded to muscularis propria or serosa, 3 patients achieved CR [66]. Interestingly, the presence of perigastric lymph nodes (< 1.5 cm) around a tumor is not a contraindication for first-line *H pylori* regimen in aforementioned two results [66]. However, Tari et al revealed that the CR rate of pure DLBCL limited to mucosa and submucosa and extended into the muscularis propria or beyond was 50% (4/8) and 0% (0/7), respectively [64]. Taken together, among 42 patients with "pure" DLBCL, tumors limited to mucosa/submucosa were marginally associated with the HP dependence (12/18 [66.7%] versus 9/24 [37.5%], p= 0.118, Fisher exact test).

In brief, the localized DLBCL/MALT with limited to submucosa has higher CR rate to HPE and the response is durable. There are several authors designed a good approach base on chromosome t(11;18) status in judging when to switch to immuno-chemotherapy or stay on watch and wait if the tumor response is not complete according to GELA definition [66]. We propose an algorithm how we treat the primary gastric lymphoma as figure 1.

Future Perspectives and Summary

The treatment paradigm of PGL is shifting from surgery to combined surgery and chemotherapy or radiotherapy, then to chemotherapy alone and finally rituximab containing chemotherapy is considered as the mainstay, however the large prospective study of HPE will show us some of this tumor can be treated by antibiotics and PPI. The practice paradigm is changing. Surgery is still important, however less popular in real world practice; it helps patients who is non-fit for chemotherapy or patients presented with bleeding or other complications hard to manage medically. Immuno-chemotherapy with R-CHOP alone achieves very high response rate and long term survival. In fact, it over shines the primary role of surgery in treating either localized or advanced PGL. Truly the outcome of advanced PGL and refractory /relapsed PGL is still dismal and the approach will depends on fitness and co-morbidity. The less will be the more or we shall consider alternative modalities. There are several novel agents showing promising result in refractory B-cell lymphoma, such as lenalidomide, bortezomib and BCL-2 inhibitors. We would like to know their efficacy in terms of extranodal lymphoma such as PGL. The salvage chemotherapy can be used but with no clinical evidence yet, the morbidity will be substantial in high dose density regimen including auto or allo-stem cell transplant. Recently an old drug but newly indicated in malignant lymphoma is bendamustine, a cytotoxic drug which has both chemical structure of cyclophosphamide and fludarabin-like purine analogue, giving less myelosupression and cardiac toxicity [67]. The combination of rituximab and bendamustine regimen currently indicated in chronic lymphocytic lymphoma, follicular lymphoma and DLBCL as well [68].

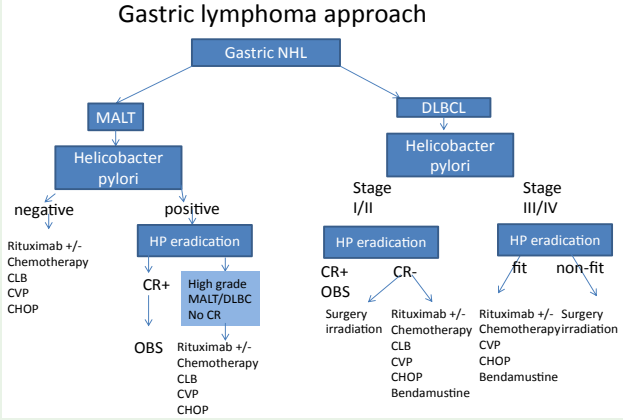

Figure 1: consider HPE first in localized MALT or DLBCL followed by chemotherapy, the surgery and radiotherapy is options for non-fit patients.

In addition to conventional treatment, the long-term efficacy of antibiotic therapy has been demonstrated in a proportional of in early-stage H. pylori-positive DLBCL of the stomach. Moreover, when antibiotics weren't curative, salvage systemic immunochemotherapy were essentially universally effective in these patients with *H pylori*-positive gastric DLBCL. Currently, TCOG is taking a step in this direction by opening a prospective phase II trial in evaluating the efficacies of first-line anti-*H pylori* regimen in the treatment of stage IE/IIE1 HP-positive gastric "pure" DLBCL patients (ClinicalTrials.gov, NCT02388581). With those new and better armamentariums, the path of cure of PGL is promising.

References

1. Tanaka T, Shimada K, Yamamoto K, Hirooka Y, Niwa Y, Sugiura I, et al. Retrospective analysis of primary gastric diffuse large B cell lymphoma in the rituximab era: a multicenter study of 95 patients in Japan. Ann Hematol. 2012; 91: 383-390.
2. Aviles A, Castaneda C, Cleto S, Neri N, Huerta-Guzmán J, Martha Gonzalez, et.al. Rituximab and chemotherapy in primary gastric lymphoma. Cancer Biotherapy & Radiopharmaceuticals. 2009; 24: 25-28.
3. Wohrer S, Puspok A, Drach J, Hejna M, Chott A, Raderer M. Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for treatment of early-stage gastric diffuse large B-cell lymphoma. Ann Oncol. 2004; 15: 1086-1090.
4. Chang MC, Huang MJ, Su YW, Chang YF, Lin J, Hsieh RK. Clinical outcome of primary gastric lymphoma treated with chemotherapy alone or surgery followed by chemotherapy. J Formos Med Assoc. 2006; 105: 194-202.
5. Isaacson PG. Gastrointestinal lymphoma. Hum Pathol. 1994; 25: 1020-1029.
6. Ferrucci PF, Zucca E. Primary gastric lymphoma pathogenesis and treatment: what has changed over thepat 10 years. Br J Hematol. 2007; 136: 521-538.
7. Delchier JC, Lamarque D, Levy M, Tkoub EM, Copie-Bergman C, Deforges L, et al. Helicobacter pyroli and gastric lymphoma: high prevalence of CagA in diffuse large B cell lymphoma but not in low grade lymphoma of mucosa-associated lymphoid tissue type. Am J Gatroenterol. 2001; 96: 2324-2328
8. Yoshino T, Omonishi K, Kobayashi K, Mannami T, Okada H , Mizuno M, et al. Clinicopathological fearture of mucosa associated lymphoid tissue (MALT) lymphoma: high grade transformation and comparison with diffuse large B cell lymphoma without MALT lymphoma features. J Clin Patho. 2000; 53: 187-190.

9. Andriani A, Zullo A, Raimondo F.DI. Clinical and endoscopic presentation of primary gastric lymphoma: a multicenter study. Aliment Pharmacol Ther. 2006; 23: 721-726.

10. Jaffe ES, Harris NL, Stein H, Vardiman JW, (Eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon; 2001.

11. d'Amore F, Brinker H, Gronbak J, Thorling K, Pedersen M, Jensen MK, et al. Non-Hodgkin's lymphoma of the gastrointestinal tract: A population-based analysis of incidence, geographic distribution, clinicopathological presentation, features, and prognosis. J Clin Oncol. 1994; 12: 1673-1684.

12. Huang J, Jiang W, Xu R, Huang H, Yue Lv, ZhongJun Xia, et.al. Primary gastric non-Hodgkin's lymphoma in Chinese patients: clinical characteristics and prognostic factors. BMC Cancer. 2012; 10: 358.

13. Mushoff K. Klinische Stadieneineteilung der Nicht-Hodgkin's Lymphoma. Strahlenther Onkol. 1977; 153: 218-221.

14. Rohatiner A, d'Amore F, Coiffier B, Crowther D, Gospodarowicz M, Isaacson P, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol 1994; 5: 397-400.

15. Salles G, Herbrecht R, Tilly H, Brousse N, Gisselbrecht C, et al. Aggressive primary gastrointestinal lymphomas: Review of 91 patients treated with the LNH-84 regimen. A study of the Group d'Etude des Lymphomes Agressifs. Am J Med. 1991; 90: 77-84.

16. Raderer M, Valencak J, österreicher C, Drach J, Hejna M, Kornek G, et al. Chemotherapy for the treatment of patients with primary high grade gastric B-cell lymphoma of modified Ann Arbor stages IE and IIE. Cancer. 2000; 88: 1979-1985.

17. Maor MH, Valesquez WS, Fuller LM, Silvermintz KB. Stomach conservation in stage IE and IIE gastric non-Hodgkin's lymphoma. J Clin Oncol. 1990; 8: 266-271.

18. Shiu MH, Nisce LZ, Pinna A, Straus DJ, Tome M, Filippa DA, et al. Recent results of multimodal therapy of gastric lymphoma. Cancer. 1986; 58: 1389-1399.

19. Sheperd FA, Evans WK, Kutas G, Yau JC , Dang P, Scott JG, et al. Chemotherapy following surgery for stage IE and IIE non-Hodgkin's lymphoma of the gastrointestinal tract. J Clin Oncol. 1988; 6: 253-260.

20. Gospodarowicz MK, Sutcliffe SB, Clark RM, Dembo AJ, Patterson BJ, Fitzpatrick PJ, et al. Outcome analysis of localized gastrointestinal lymphoma treated with surgery and postoperative irradiation. Int J Radiation Oncology Biol Phys. 1990; 19: 1351-1355.

21. Rosen C, Heerden JA, Martin LK, Wold LE, Ilstrup DM. Is an aggressive surgical approach to the patient with gastric lymphoma warranted? Ann Surg. 1987; 205: 634-640.

22. Hockey MS, Powel J, Crocker J, Fielding JWL. Primary gastric lymphoma. Br J Surg. 1987; 74: 483-487.

23. Schwarz RJ, Conners JM, Schmidt N, et al. Diagnosis and management of stage IE and stage IIE gastric lymphomas. Am J Surg. 1993; 165: 561-565.

24. Durr ED, Bonner JA, Strickler JG, Martenson JA, Chen MG, Habermann TM, et al. Management of stage IE primary gastric lymphoma. Acta Haematol. 1995; 94: 59-68.

25. Yoon SS, Coit DG, Portlock CS, Karpeh MS. The diminishing role of surgery in the treatment of gastric lymphoma. Ann Surg. 2004; 240: 28-37.

26. Avilés A, Nambo MJ, Neri N, Huerta-Guzmán J, Cuadra I, Alvarado I, et al. The role of surgery in primary gastric lymphoma: Results of a controlled clinical trial. Ann Surg. 2004; 240: 44-50.

27. de Jong D, Aleman BMP, Taal BG, et al. Controversies and consensus in the diagnosis, work-up and treatment of gastric lymphoma: an international survey. Ann Oncol. 1999; 10: 275-280.

28. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM,et al. Chemotherapy alone compared chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med. 1998; 339: 21-26.

29. Sheridan WP, Medley G, Brodie GN. Non-Hodgkin's lymphoma of the stomach: A prospective pilot study of surgery plus chemotherapy in early and advanced disease. J Clin Oncol. 1985; 3: 495-500.

30. Cooper DC, Doria R, Salloum E. Primary gastrointestinal lymphomas. Gastroenterologist. 1996; 4: 54-64.

31. Ruskoné-Fourmestraux A, Aegerter P, Delmer A, Brousse N, Galian A, Rambaud JC, et al. Primary digestive tract lymphoma: A prospective multicentric study of 91 patients-Group d'Etude des Lymphoma Digestifs. Gastroenterology. 1993; 105: 1662-1671.

32. Gobbi PG, Dionigi P, Barbieri F, Corbella F, Bertoloni D, Grignani G, et al. The role of surgery in the multimodal treatment of primary gastric non-Hodgkin's lymphoma: A report of 76 cases and review of the literature. Cancer. 1990; 65: 2528-2536.

33. Bellesi G, Alterini A, Messori A, Bosi A, Bernardi F, di Lollo S, et al. Combined surgery and chemotherapy for the treatment of primary gastrointestinal intermediate- or high-grade non-Hodgkin's lymphomas. Br J Cancer. 1989; 60: 244-248.

34. Tondini C, Giardini F, Bezztti P, Valagussa P, Santoro A, Bertulli R, et al. Combined modality treatment for primary gastrointestinal non-Hodgkin's lymphoma: The Milan Cancer Institute experience. Ann Oncol. 1993; 4: 831-837.

35. Rackner VL, Thirlby, Ryan JA. Role of surgery in multimodality therapy for gastrointestinal lymphoma. Am J Surg. 1991; 161: 570-575.

36. Liu HT, Hsu C, Chen CL, Chiang IP, Chen LT, Chen YC, et al. Chemotherapy alone versus surgery followed by chemotherapy for stage I/IIE large-cell lymphoma of the stomach. Am J Hematol. 2000; 64: 175-179.

37. Coiffier B, Gisselbrecht C, Herbrecht R, H Tilly, A Bosly, N Brousse. LNH-84 regimen: A multicentric study of intensive chemotherapy in 737 Patients with aggressive malignant lymphoma. J Clin Oncol. 1989; 7: 1018-1026.

38. Nakamura S, Matsumoto T, Iida M, Yao T, Tsuneyoshi M. Primary gastric lymphoma in Japan: A clinicopathologic analysis of 455 patients with special reference to its time trends. Cancer. 2003; 97: 2462-2473.

39. Ho CL, Hsieh AT, Dai MS, Chen YC, Kao WY, Chao TY. Non-Hodgkin's lymphoma of the stomach: treatment outcomes for 57 patients over a 20-year period. J Chin Med Assoc. 2005; 68: 11-15.

40. Binn M, Rouskoné-Fourmestraux A, Lepage E, et al. Surgical resection plus chemotherapy versus chemotherapy alone: Comparison of two strategies to treat diffuses large B-cell lymphoma. Ann Oncol. 2003; 14: 1751-1757.

41. Vaillant JC, Ruskoné-Fourmestraux A, Aegerter P, Gayet B, Rambaud JC, Valleur P, et al. Management and long-term results of surgery for localized gastric lymphomas. Am J Surg. 2000; 179: 216-222.

42. Koch BP, del Valle F, Berdel WE, Willich NA, Reers B, Hiddemann W, et al. Primary gastrointestinal non-Hodgkin's lymphoma: II. Combined surgical and conservative or conservative management only in localized gastric lymphoma-results of the prospective German multicenter study GIT NHL 01/92. J Clin Oncol. 2001; 19: 3874-3878.

43. Coiffier B, Gisselbrecht C, Bosly A, Herbrecht R, Bouabdallah R, Morel P, et al. Ten years follow-up of the GELA LNH98.5 Study, first randomized study comparing R-CHOP to CHOP chemotherapy in patients with diffuse large B-cell lymphoma. ASH. 2009; 114: 3741.

44. Lv Y, Wang XN, Liang H. Clinical analysis of 200 patients with primary gastric lymphoma. Zhonghua Wei Chang Wai Ke Za Zhi. 2012; 15: 157-160.

45. Selçukbiricik F, Tural D, Elicin O, Berk S, Ozguroglu M, Bese N, et al. Primary gastric lymphoma: conservative treatment modality is not inferior to surgery for early-stage disease. ISRN Oncol. 2012; 95: 1816.

46. Ruskoné-Fourmestraux 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.

47. Chen LT, Lin JT, Tai JJ, Chen GH, Yeh HZ, Yang SS, et al. Long-term results of anti-Helicobacter pylori therapy in early-stage gastric high-grade transformed MALT lymphoma. J Natl Cancer Inst. 2005; 97: 1345-1353.

48. Nakamura S, Matsumoto 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: 454-460.

49. Ng WW, Lam CP, Chau WK, Fen-Yau Li A, 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: 93-96.

50. Cavanna L, Pagani R, Seghini P, Zangrandi A, Paties C. High grade B-cell gastric lymphoma with complete pathologic remission after eradication of helicobacter pylori infection: Report of a case and review of the literature. World J of Surgical Oncol. 2008; 6: 35.

51. Zullo A, Hasson C, Cristofari F, Andriani A, De Francesco V, Ierardi E, et al. Effects of helicobacter pylori eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. Clin gastroenterol Hepatol. 2010; 8: 105-110.

52. Kuo SH, Cheng AL. Helicobacter pylori and mucosa-associated lymphoid tissue: what's new. Hematology Am Soc Hematol Educ Program. 2013; 2013: 109-117.

53. Chen LT, Lin JT, Shyu RY, Jan CM , Chen CL, Chiang IP, et al. Prospective study of Helicobacter pylori eradication therapy in stage I (E) high-grade mucosa-associated lymphoid tissue lymphoma of the stomach. J Clin Oncol. 2001; 19: 4245-4251.

54. Morgner A, Miehlke S, Fischbach W, Schmitt W, Hermelink HM, 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: 2041-2048.

55. 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: 1207-1212.

56. Alpen B, Röbbecke J, Wündisch T, Stolte M, Neubauer A. Helicobacter pylori eradication therapy in gastric high grade non Hodgkin's lymphoma (NHL). Ann Hematol. 2001; 80: 106-107.

57. Matolcsy A, Nagy M, Kisfaludy N, Kelényi G. Distinct clonal origin of low-grade MALT-type and high-grade lesions of a multifocal gastric lymphoma. Histopathology. 1999; 34: 6-8.

58. Kuo SH, Chen LT, Wu MS, Kuo KT, Yeh KH, Doong SL, et al. Differential response to H. pylori eradication therapy of co-existing diffuse large B-cell lymphoma and MALT lymphoma of stomach-significance of tumour cell clonality and BCL10 expression. J Pathol. 2007; 211: 296-304.

59. Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood. 2008; 112: 4384-4399.

60. Swerdlow SH, Campo E, Harris NL, et al. The World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: WHO; 2008.

61. Suzuki T, Matsuo K, Ito H, Hirose K, Wakai K, Saito T, et al. A past history of gastric ulcers and Helicobacter pylori infection increase the risk of gastric malignant lymphoma. Carcinogenesis. 2006; 27: 1391-1397.

62. Tari A, Asaoku H, Kashiwado K, Yoshino T, Kitadai Y, Tanaka S, et al. Predictive value of endoscopy and endoscopic ultrasonography for regression of gastric diffuse large B-cell lymphomas after Helicobacter pylori eradication. Dig Endosc. 2009; 21: 219-227.

63. Kuo SH, Yeh KH, Wu MS, Lin CW, Hsu PN, Wang HP, et al. Helicobacter pylori eradication therapy is effective in the treatment of early-stage H pylori-positive gastric diffuse large B-cell lymphomas. Blood. 2012; 119: 4838-4844.

64. Doglioni C, Ponzoni M, Ferreri A, Savio A. Gastric lymphoma: The histology report. Digestive and Liver Disease. 2011; 43: 310-318.

65. Zullo A, Hassan C, Andriani A, Cristofari F, De Francesco V, Ierardi E, et al. Eradication therapy for Helicobacter pylori in patients with gastric MALT lymphoma: a pooled data analysis. Am J Gastroenterol. 2009; 104: 1932-1937.

66. Ferreri AJ, Govi S, Raderer M, Mulè A, Andriani A, Caracciolo D, et al. Helicobacter pylori eradication as exclusive treatment for limited-stage gastric diffuse large B-cell lymphoma: results of a multicenter phase 2 trial. Blood. 2012; 120: 3858-3860.

67. Cheson B, Rummel M. Bendamustine rebirth of an Old Drug. J Clin Oncol 2009:1492-1501.

68. Rummel M, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, Josten KM, et.al. Bedamustine plus rituximab is effective as favorable toxicity profile in the treatment of mantle cell and low grade non-Hodgkin's lymphoma. J Clin Oncol. 2005; 23: 3383-3389.