

Primary gastric lymphoma pathogenesis and treatment: what has changed over the past 10 years?

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Summary

Primary gastric (PG) lymphomas are generally non-Hodgkin lymphomas (NHL). They represent 5% of gastric malignancies and show an apparently increasing incidence worldwide. The most common histological subtypes are diffuse large B-cell and marginal zone B-cell NHL of the mucosa-associated lymphoid tissue (MALT)-type. Pathogenesis is often related to *Helicobacter pylori* infection (HPI). There is still no consensus on the optimal treatment for PG lymphoma. Nowadays surgery is limited to rare cases and radiotherapy – combined or not with chemotherapy – represents an effective therapeutic option ensuring long-term, organ-salvage benefits mainly in aggressive histological subtypes. Additionally, the description of MALT lymphomas has made the situation even more complex, because antibiotics alone can induce lasting remissions in those cases associated with HPI. Consequently, a global therapeutic approach to the cure of PG-NHL has completely changed over the last 10 years: innovative, conservative options to reduce treatment toxicity, thus preventing systemic relapses, have made their appearance and are on the rise.

Keywords: extra-nodal lymphomas, primary gastric lymphomas, mucosa-associated lymphoid tissue lymphomas, *Helicobacter pylori* infection.

Lymphomas represent a frequent cause of death from cancer in industrialised western countries, and its occurrence has been constantly on the rise over the last two to three decades. According to data from SEER (*Surveillance, Epidemiology and End Results*), incidence has increased by approximately 80% in the USA from 1973 (Parkin *et al*, 1999; Gurney & Cartwright, 2002). This increase appears to be higher in extra-nodal rather than in nodal forms (Groves *et al*, 2000; Chiu & Weisenburger, 2003).

Extra-nodal forms account for approximately 1/4 to 1/2 of the total number of cases (Zucca *et al*, 1997) and are

primarily represented by non-Hodgkin lymphoma (NHL) of the central nervous system (CNS), followed by gastric, intestinal and cutaneous lymphomas (Devesa & Fears, 1992; Groves *et al*, 2000). Statistics similar to those in the USA have also been reported in European countries (Moller *et al*, 2004).

The gastro-intestinal tract is frequently involved, representing 30–40% of extra-nodal lymphomas and from 4–20% of all NHL cases (d'Amore *et al*, 1991; Herrmann *et al*, 1980).

In Western countries, the most commonly affected site is the stomach (approximately 50–60%), followed by the small intestines (30%) and the large intestines (around 10%). Involvement of the oesophagus is, on the other hand, quite rare. The segments most affected in the small intestines – in decreasing order of frequency – are the ileocaecal site, jejunum and duodenum.

With respect to gastric involvement, NHL represents the most frequent tumour, following adenocarcinoma (Hockey *et al*, 1987); on the contrary, primary and secondary involvement of the stomach is extremely rare in Hodgkin disease (Venizelos *et al*, 2005).

The real increase of NHL incidence in the gastro-intestinal tract during the last two decades is uncertain as one cannot exclude a correlation with improvements in diagnostic procedures over this same period (Hayes & Dunn, 1989; Severson & Davis, 1990; Devesa & Fears, 1992; Gurney *et al*, 1999).

An epidemiological analysis carried out in comparable demographic areas in the UK and northern Italy showed a higher incidence of gastric NHL in the North-eastern regions of Italy ($13.2 \times 10^5/\text{year}$ vs. $1 \times 10^5/\text{year}$). This suggests the existence of geographical variations, perhaps correlated to the rate of chronic gastritis caused by *Helicobacter pylori* (HP) in the regions under examination (Doglioni *et al*, 1992).

In a group of diseases as heterogeneous as this (as far as clinical presentation, response-to-treatment and prognosis are concerned), the need for useful classifications during the diagnostic-therapeutic procedures has always been felt. Apropos, the definition itself of a primary extra-nodal lymphoma has also represented a crucial problem that, at least in part, can explain the wide variation in incidence rates for the primary extra-nodal forms in the literature.

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Dawson *et al* (1961) first described gastro-intestinal lymphomas using restricted criteria, such as the presence of a predominant gastro-intestinal lesion, with or without expansion to regional lymph nodes but without involvement of distal lymph nodes; this definition also excluded cases with leukaemic presentation and those with bone marrow, spleen or liver involvement. This definition was later expanded (Lewin *et al*, 1978; Herrmann *et al*, 1980) to include cases involving the adjacent liver and spleen.

The literature also carries other wider definitions, i.e. a primary extra-nodal lymphoma is such when, following complete staging, it presents a predominant extra-nodal component (superior to 75% of total tumour volume) associated or not with a smaller nodal component that must, however, represent less than 25% of tumour volume (d'Amore *et al*, 1991).

Histology and pathogenesis

General histological and immunophenotypic characteristics

Non-Hodgkin lymphomas histological classification has been one of the most controversial problems in the field of Haematology. Primary extra-nodal forms were specifically taken into consideration for the first time in 1994, with the REAL classification (Revised European-American Lymphoma Classification) – the first to identify different clinical–pathological realities according to all the information available at that time: morphological, immunophenotypic, genetic and clinical (Harris *et al*, 1994). The World Health Organization (WHO) classification originates directly from the REAL classification and distinguishes over 30 different forms, and, as a result, constitutes a very heterogeneous group of lymphoproliferative tumours having a wide variety of biological, clinical and response-to-treatment behaviour patterns (Jaffe *et al*, 2001).

Two histological types are particularly frequent in primary extra-nodal presentations. In fact, as opposed to their nodal counterpart, they are characterised by a preponderance of diffuse large B-cell lymphomas and marginal zone B-cell lymphomas of the MALT-type (an acronym for 'Mucosa-Associated Lymphoid Tissue' and therefore extra-nodal by definition). Follicular, mantle cell and peripheral T-cell lymphomas are hardly represented at all (Zucca *et al*, 1997, 1999; Table I).

The ability of mature lymphocytes to re-circulate between blood and the lymph is probably implicated in the determination of the specific location of extra-nodal forms. Interaction between circulating lymphocytes and endothelial venules, mediated by receptor molecules (lymphocytic integrins, which recognise tissue-specific molecules called addressins), has been demonstrated. Known as 'lymphocytic homing', this mechanism appears to be extremely important in several types of cutaneous and gastro-intestinal tract extra-nodal lymphomas. In MALT-type lymphomas of the gastro-

Table I. Distribution of the main histological types (defined according to the criteria in the REAL classification) in 393 patients with a localised gastric lymphoma that were enrolled in the German multi-centre perspective study for gastrointestinal NHL (GIT NHL 02/96) (Koch *et al*, 2005).

Histological type	Frequency (%)
Diffuse large B-cell lymphoma	59
With MALT component	14
Without MALT component	45
MALT lymphoma of the marginal zone	38
Mantle lymphoma	1
Follicular lymphoma	0.5
Peripheral T-cell lymphoma	1.5

intestinal tract, the integrin $\alpha 4\beta 7$, a 'mucosal homing receptor', has been identified on the neoplastic cells; this 'receptor' binds the cellular adhesion molecule MAdCAM-1 (mucosal addressin cell adhesion molecule-1), a vascular addressin selectively expressed by the endothelium of the mucous membranes (Dogan *et al*, 1997; Drilenburg *et al*, 1997; Drilenburg & Pals, 2000).

In 1983, after observing that some cases of low-grade malignant gastro-intestinal lymphomas had morphological characteristics closer to those of Payer's patches rather than those of lymph nodes affected by an indolent lymphoma, Isaacson and Spencer proposed, for the first time, the concept of a MALT-type lymphoma (Isaacson, 1995). MALT lymphomas represent the most frequent histotype in low-grade malignant primary gastric lymphomas (Table I). This extra-nodal lymphoma develops from B-lymphocytes of the marginal zone and is characterised by a cellular population that can have heterogeneous aspects, with the presence of small lymphocytes (often centrocytic-looking) or lymphocytes with a monocytoid appearance. A variable number of large cells (immunoblasts and centroblasts) is usually present (Zucca *et al*, 1998a). Plasma-cell differentiation is present in about 1/3 of gastric MALT-type lymphomas and is usually more prominent in thyroid and small intestinal localisations (Isaacson *et al*, 2001). The tumour-B cells in glandular tissues can often invade and destroy crypts and glands, causing distinctive, lymphoepithelial lesions (Fig 1) (Zucca *et al*, 1998a; Isaacson *et al*, 2001).

Reactive follicles can be present, and their germinal centres are sometimes colonised by the lymphoma cells (Isaacson *et al*, 2001).

An increased number of large cells in a MALT lymphoma can, at times, create problems from a diagnostic point of view, suggesting a histological transformation into a diffuse large B-cell lymphoma – a transformation that is usually defined by the presence of compact aggregates or a sheet-like proliferation of large cells (Isaacson *et al*, 2001).

High-grade primary gastric lymphomas are nearly always of the B-phenotype and are characterised by an aggressive clinical–pathological presentation.

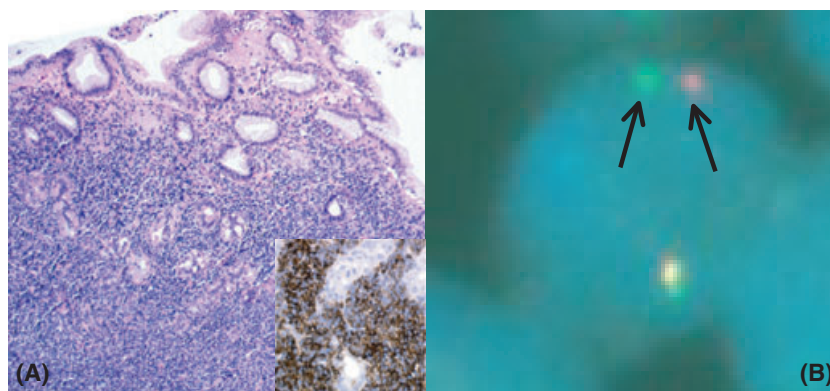


Fig 1. Histological aspects of primary gastric lymphoma as seen in a gastric biopsy of a mucosa-associated lymphoid tissue (MALT)-type lymphoma: the invasion and destruction of the glands by tumoural small- and medium-sized lymphocytes (A, original magnification $\times 10$), immuno-reactive for CD20, causing the formation of distinctive lymphoepithelial lesions (A, inset, original magnification $\times 40$) on the gastric glands. Interphase fluorescent *in situ* hybridisation using the LSI MALT1 Dual Color Breakapart DNA probe shows split signals in most of the nuclei analysed, a pattern consistent with the occurrence of a 18q21 locus translocation involving the MALT1 gene (B). Courtesy of Dr G. Pruneri, Department of Pathology, European Institute of Oncology.

Whether all diffuse large B-cell gastric lymphomas are derived from previous low-grade MALT lymphomas is still an open question that is not yet resolved unequivocally. It should be remembered, however, that the cytogenetic alterations common in gastric MALT lymphomas are different from those typical of large-cell primary lymphomas of the stomach (Starostik *et al*, 2000, 2002). According to the most recent WHO classification, the term 'high-grade MALT lymphoma' should not be used, while the diction 'MALT lymphoma' should be restricted only to a low-grade lymphoma made up principally of small cells (Isaacson *et al*, 2001).

From an immunophenotypic point of view, a specific antigenic profile of MALT lymphomas does not exist. The B-cells in MALT lymphomas show an immunophenotype identical to that of the marginal zone B-cells present in the spleen, Payer's patches and lymph nodes (Isaacson *et al*, 2001). In particular, they present a surface positivity for immunoglobulins, for pan-B antigens (CD19, CD20, CD79a) and for antigens typical of the marginal zone (CD35, CD21). Moreover, they are negative for CD5, CD10, CD23 and cyclin D1.

The reactive T-lymphocytic component, which is often rich in MALT lymphoma, can be identified by searching for CD3, CD4 and CD8. T cells seem important in the initial phase of a MALT lymphoma's development and are usually less numerous in diffuse large B-cell lymphomas (Zucca *et al*, 1998a).

Lymphoepithelial lesions can be identified by using anti-CD20 antibodies and anti-pan-cytokeratin, while anti-CD23 and anti-CD35 antibodies mark follicular dendritic cells, allowing for the identification of reactive follicles.

Pathogenesis of B-cell MALT gastric lymphomas

Association with chronic HPI. Mucosa-associated lymphoid tissue lymphomas represent 7–8% of all B-cell lymphomas and approximately 50% of primary gastric lymphomas (Fischbach

et al, 1992). They originate in the stomach from lymphatic tissue that, in association with the mucous membrane, usually develops following chronic *Helicobacter pylori* infection (HPI). In fact, lymphatic tissue is not present in a normal gastric mucous membrane (Zucca *et al*, 2000). The first studies published showed presence of the bacteria in over 90% of cases (Wotherspoon *et al*, 1991); nonetheless, subsequent clinical series reported a lower incidence, showing that the density and presence of the germ itself may lessen during the evolution from chronic gastritis to lymphoma. In a Japanese study (Nakamura *et al*, 1997), HP was detected in 145 of 237 patients (61%) with gastric lymphomas. The presence of HP was significantly more frequent in patients with a lymphoma restricted to the mucosa and submucosa (76%) than in those with a lymphoma invading beyond the submucosa (48%); it was also more common in patients with MALT lymphomas (72%) than in those with high-grade tumours (55%). Moreover, the frequency of HP positivity was significantly lower in gastric lymphoma cases than in chronic active gastritis (100%) or peptic ulcer cases (91%) (Nakamura *et al*, 1997).

Furthermore epidemiological evidence of an aetiopathogenetic link to HPI was provided by a large case-control study, which showed a statistically significant association between previous HPI and the development of a primary gastric lymphoma, either with a low-grade (MALT-type) or a high-grade (diffuse large-cell) histology (Parsonnet *et al*, 1994). Although HP infects over 50% of the world's population, most patients with HPI do not develop lymphomas; therefore, it is commonly believed that additional environmental, microbial or host genetic factors may play a role in gastric lymphomagenesis. Infection with HP strains that carry the cytotoxin-associated antigen A (*cagA*) is linked to gastric carcinoma (Ahmed & Sechi, 2005), and it has been suggested that *cagA*-positive strains may also be associated with lymphoma development. But, available data are contradictory, as discussed later.

The aetiopathogenetic correlation between HP and lymphomas has been confirmed on a biological as well as molecular level, both through gastric biopsies (carried out years before the onset of a lymphoma in patients having a long history of chronic gastritis) showing the presence of B-lymphocytic clones that will later give origin to the tumour (Zucca *et al*, 1998b) and through the ability to induce growth of the lymphomatous cells *in vitro* when stimulated by HP under culture (Hussell *et al*, 1993, 1996). Additionally, it is now known that HP eradication through antibiotics is able to induce remission of a gastric MALT lymphoma in the majority of cases (Zucca & Cavalli, 2004; Bertoni & Zucca, 2005).

Epidemiological (Parsonnet *et al*, 1994) and experimental data (Hussell *et al*, 1993, 1996) support the hypothesis that this microorganism can represent an antigenic stimulus able to sustain the growth of a gastric lymphoma (Zucca & Cavalli, 2004; Bertoni & Zucca, 2005). Somatic hyper-mutations and the intra-clonal variation observed in the genes of the immunoglobulins in a gastric B-cell MALT lymphoma suggest that the tumoural cells have undergone an antigenic selection in the germinal centres and that subsequent clonal expansion continues to be guided directly (at least partially) by antigenic stimulation (Bertoni *et al*, 1997). A recent observation that a gastric MALT lymphoma is associated with polymorphisms in those genes regulating both the inflammatory response and anti-oxidative mechanisms seems to suggest a correlation with individual variations of the inflammatory response to HP and the capacity to neutralise free radicals (Rollinson *et al*, 2003; Ye

et al, 2003). Figure 2 summarises schematically the phases in the development and progression of a MALT lymphoma according to a model that was proposed initially by Isaacson (Isaacson, 1995).

A favourable clinical course has, in the past, resulted in the evaluation of many gastric MALT lymphomas as 'pseudo-lymphomas'. Nevertheless, several characteristics underline their neoplastic nature: an often-demonstrated monoclonality; the presence of recurrent chromosomal aberrations; the potential to evolve towards high-grade forms; and possible dissemination to lymph nodes or other extra-nodal sites (Zucca *et al*, 1998a).

Genetic and molecular alterations. In MALT lymphomas, at least three recurrent chromosomal translocations have been identified, and together are present in approximately 65% of cases: the t(11;18)(q21;q21) translocation, which causes the formation of the chimaeric fusion gene *API2-MALT1*; the t(1;14)(p22;q32) translocation, which causes the deregulation of *BCL10*; and the t(14;18)(q32;q21) translocation, causing the deregulation of *MALT1*. Though involving different genes, all these translocations result in the activation of the nuclear transcription factor NfκB (nuclear factor κB), which has a central role in the regulation of the various genes involved in immunity, inflammation and apoptosis (Cavalli *et al*, 2001; Isaacson & Du, 2004; Zucca & Bertoni, 2005). Consequently, NFκB activation appears able to make a relevant contribution to the growth and progression of MALT lymphomas. Other

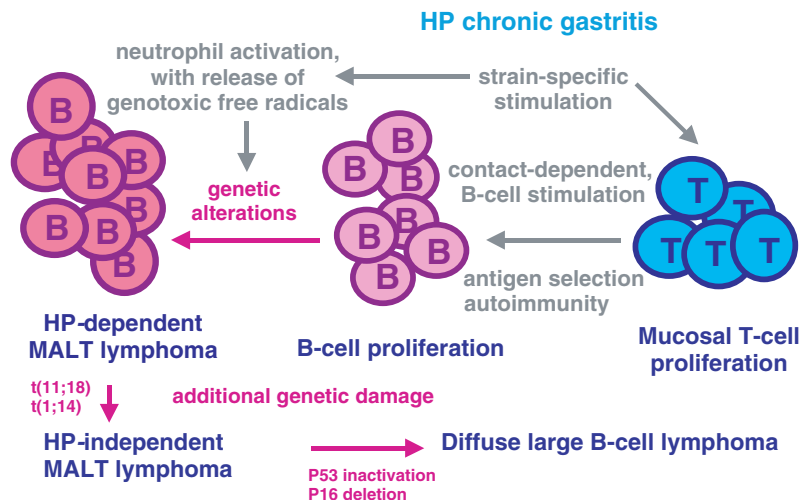


Fig 2. Schematic model of the origin and progression of a mucosa-associated lymphoid tissue (MALT) lymphoma. HPI stimulates the formation of lymphocytic infiltration of the gastric mucous membrane. As a result of direct antigenic stimulation and indirect stimulation (T-cells specific for HP), B-cells proliferate and can, at times, undergo a neoplastic transformation following the acquisition of genetic abnormalities, perhaps facilitated by the presence of free radicals. The accumulation of genetic abnormalities is associated with both a loss of dependency (as a result of antigenic stimulation) as well as a possible histological transformation. Tumours having a t(11;18)(q21)/*API2-MALT1* translocation do not respond to eradication of the infection, but they are rarely transformed into diffuse large B-cell lymphomas. Even lymphomas with a t(1;14) translocation appear to be independent of antigenic stimulation, yet they can undergo histological transformations. Tumours without these translocations present other genetic lesions that often respond to antibiotics; but they, too, can progress and become HP-independent, eventually transforming themselves into large-cell lymphomas following the inactivation of p53 and p16.

genetic alterations identified in gastric MALT lymphomas include trisomy of chromosome 3, mutations or the loss of heterozygosity in p53 and deletions of p16 (Zucca *et al*, 2000).

Present in approximately a third of MALT lymphomas, the most frequent translocation is t(11;18)(q21;q21), with an incidence that is variable according to the disease site: it is quite common in lung and gastric localisations but more rare in other sites (Ye *et al*, 2003). Identification of the t(11;18)(q21;q21) translocation could have important clinical implications. In fact, lymphomas carrying this genetic alteration do not respond to antibiotic therapy aimed at eradicating HPI and are often diagnosed in a more advanced phase (Liu *et al*, 2001a,b, 2002). On the other hand, this translocation seems to be associated with a low risk of both an onset of additional genetic damage as well as histological transformation into a large-cell aggressive lymphoma (Cavalli *et al*, 2001; Starostik *et al*, 2002).

The t(14;18)(q32;q21) translocation involves genes in the heavy chains of immunoglobulins and the *MALT1* gene. It is present in approximately 20% of MALT lymphomas, and its incidence appears to vary according to the disease site, being common in lymphomas localised in the salivary glands and ocular adnexa but extremely rare in the gastro-intestinal tract (Sanchez-Izquierdo *et al*, 2003; Streubel *et al*, 2003).

Though only in very few cases, the t(1;14)(p22;q32) translocation has been found exclusively in MALT lymphomas (Cavalli *et al*, 2001). This translocation has been shown to deregulate BCL10 expression in the nucleus of neoplastic B-cells, with a resulting increase in NFkB activation (Isaacson & Du, 2004).

Molecular events that follow all these translocations have the NFkB factor as their final target. In physiological conditions, the binding between BCL10 and MALT1 is crucial in the oligomerisation and self-activation of MALT1, which leads to NFkB activation. In contrast to a normal MALT1 protein, the AP12-MALT1 fusion protein seems to possess a self-oligomerisation mechanism capable of activating NFkB independently from BCL10 (Isaacson & Du, 2004; Zucca & Bertoni, 2005).

The presence of these three different structural aberrations of the karyotype (all connected to the same histological type and to the activation of the same signalling pathway) in MALT lymphomas having onsets in differing anatomical sites seems to suggest the possibility of 'site-specific' paths for MALT-lymphoma development in different organs and tissues (Zucca & Bertoni, 2005).

It is likely that both additional bacterial and host individual factors interact to cause a lymphoma. Polymorphisms affecting genes, such as *IL1RN* and *GSTT1* (which are involved in inflammatory responses and antioxidative capacity), may represent at least part of the genetic background for lymphomagenesis in HPI individuals (Rollinson *et al*, 2003). Free radicals are likely to play a role in the development of B-cell genomic damage in chronic gastritis, and their presence is increased with the presence of the CagA-positive strains of HP. In fact, HP strains expressing the CagA protein appear to

be more aggressive, inducing either more severe gastritis or peptic ulcerations, and they have also been associated with the development of gastric adenocarcinoma (Ahmed & Sechi, 2005). The finding of anti-CagA antibodies in almost all cases of MALT lymphomas at a significantly higher rate than in active gastritis cases led to the hypothesis that CagA⁺ HP strains could be linked to the development of gastric MALT lymphomas (Eck *et al*, 1997). Another study found a significantly high frequency of CagA⁺ strain infections in high-grade gastric lymphomas, suggesting a possible role in their histological transformation (Peng *et al*, 1998). However, additional studies (de Jong *et al*, 1996; van Doorn *et al*, 1999; Taupin *et al*, 1999) were unable to find any correlation. Hence, the pathogenetic role of the CagA protein remains controversial. More recently, the chromosomal translocation t(11;18)(q21;q21) was found to be closely related to infection by CagA-positive strains in gastric MALT lymphomas. It has therefore been hypothesised that oxidative damage might play a role in the development of this genetic alteration (Ye *et al*, 2003). As previously mentioned, the t(11;18)(q21;q21) occurs at markedly variable frequencies in MALT lymphomas at different sites, suggesting that the occurrence of this translocation may be influenced by a premalignant local environment.

Pathogenesis of DLBC gastric lymphomas

In a high percentage of extra-nodal high-grade lymphomas, the oncogene *BCL6* (located on chromosome 3q27) is altered due to translocations, somatic hyper-mutations or deregulating mutations involving the promoter region. These re-arrangements induce an over-expression of the gene, which seems to predict a better prognosis (Offit *et al*, 1994). This information also appears to be true for diffuse large B-cell (DLBC) gastric lymphomas which, analogous to a DLBCL developing in any other site, can be immuno-histochemically subclassified into at least two subgroups: GCB (germinal centre B-cell-like) and non-GCB DLBCL. In gastric large-cell lymphomas, high BCL-6 expression was detected in all GCB cases, irrespective of *BCL6* genetic alterations. In the non-GCB subgroup, *BCL6* deregulating mutations correlated significantly with a high BCL-6 expression level. No noteworthy correlation was found between the BCL-6 expression level and survival in the non-GCB cases, which had significantly poorer outcomes than the GCB subgroup (Chen *et al*, 2006).

Interestingly, BCL-2 protein expression was found to be notably lower in gastric than in non-gastric primary extra-nodal high-grade B-cell lymphomas, while nuclear p53 protein expression did not differ significantly between these two groups (Cogliatti *et al*, 2000). There were no meaningful differences in either BCL-2 or p53 expression profiles between large-cell lymphomas of the stomach (with or without evidence of a low-grade MALT-type component). However, in DLBCL with a low-grade MALT component, a significant downregulation of BCL-2 – and, conversely, an upregulation of

p53 protein ($P < 0.0001$) – was found in high-grade areas when compared with their low-grade tumour components. In extra-nodal high-grade B-cell lymphomas, BCL-2 protein expression was not associated with a t(14;18) translocation. These findings suggest that primary gastric DLBCL may be distinct from primary extra-nodal high-grade B-cell lymphomas occurring outside the stomach (Cogliatti *et al*, 2000). Indeed, *de novo*, gastric large-cell lymphomas and those derived from a low-grade MALT lymphoma may develop along distinct pathogenetic pathways (Starostik *et al*, 2000).

Clinical aspects

Signs and symptoms

Regardless of histological typing, the initial symptomatology of a gastric lymphoma is often quite unspecific and more evocative of gastritis or an ulcerous condition rather than a neoplasm; for this reason, its diagnosis is often delayed.

The most common symptoms are epigastric pain and dyspepsia, with nausea and vomiting, anorexia and weight loss being also very frequent. B-symptoms are extremely rare. Gastro-intestinal haemorrhaging (haematemesis or melena) occurs at the outset in 20–30% of patients, while gastric occlusion and perforation are quite uncommon (Cogliatti *et al*, 1991; Radaszkiewicz *et al*, 1992; Koch *et al*, 2001a). An objective examination is normal in 55–60% of patients, while abdominal masses and/or peripheral lymphadenopathy can be felt when the disease is at an advanced stage, especially in cases where the histology is aggressive.

Diagnostic procedures

Diagnosis is usually carried out by the examination of a biopsy specimen taken during an oesophageal-gastro-duodenoscopy. Other radiological studies of the upper digestive tract could also prove useful, but, given its uniqueness, an endoscopic

evaluation – which could show slight and unspecific alterations in the mucous membrane, the presence of a mass or a polypoidal lesion with or without an ulcer (Fig 3) – is always to be preferred.

The most frequent sites of a gastric lymphoma are at the pyloric antrum, corpus and cardias. The extension of a duodenal lesion through the pylorus is evocative of a lymphoma, but it is not pathognomonic; for this reason, verification through biopsy is always deemed necessary.

At times, should the specimen not be sufficiently deep, histopathology may prove inconclusive as there are lymphomas that infiltrate the submucosa without involving the mucous membrane. In addition, it must be remembered that, as far as the stomach is concerned, a MALT lymphoma is quite often multi-focal (Wotherspoon *et al*, 1992).

Accurate, local staging requires an endoscopy with multiple biopsies in each region of the stomach, duodenum and at the gastro-oesophageal junction, as well as in any area having an abnormal showing. It is essential to collect an adequate quantity of material for histopathological and immunohistochemical verifications.

As previously stated, identification of the t(11;18) translocation is important in the diagnosis of illnesses that are unresponsive to antibiotics, and this can be carried out by fluorescent *in situ* hybridisation on fixed material (Liu *et al*, 2001a,b). To demonstrate genetic alterations, molecular biology can help define diagnosis in those rare cases of uncertainty.

The presence of active HPI must be determined through histochemistry, a rapid testing of the urease enzyme levels ('breath-test'). When the latter is negative, it is helpful to turn to serology, which could show previous infection even though the bacteria is currently absent.

Staging procedures

Once a diagnosis has been made (and before any therapeutic decision has been taken), it is important to establish the

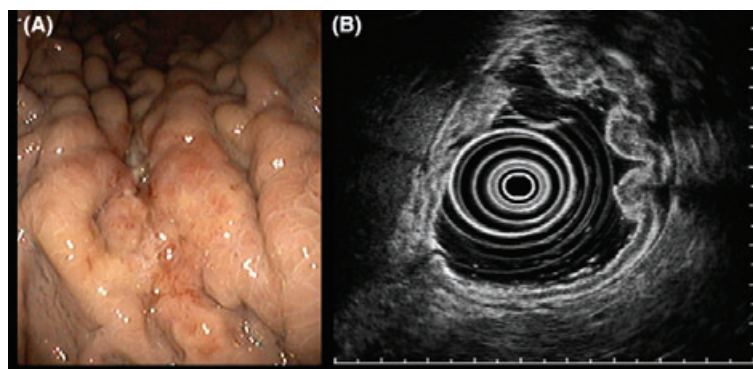


Fig 3. (A) An endoscopic aspect of a mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach: gastric folds are prominent, unable to be extended, with a small ulcer along the greater curvature of the gastric body. (B) Ultrasound-endoscopy investigation of the same MALT patient shows thickening of the wall, with fusion of the normal stratification due to involvement of the mucosa, sub-mucosa and muscularis-mucosa membranes, whose external margins appear to be reasonably regular. Courtesy of Dr M. De Boni, Department of Gastroenterology, ULSS Feltre Hospital.

disease's anatomical extension as this is a crucial prognostic factor.

The problem of 'staging' a gastric lymphoma is controversial even today (Rohatiner *et al*, 1994; de Jong *et al*, 1997). In fact, various staging systems are still in use. In 1993, an international 'workshop' that was specifically centred around this theme proposed a modification – known as 'Lugano staging' (Rohatiner *et al*, 1994) (Table II) – to Blackledge's system.

It is essential to complete endoscopic staging with a computed tomography (CT)-scan of the chest and abdomen in order to exclude systemic, lymph-nodal extension and/or infiltration of the adjacent structures. An endoscopic ultrasound (Fig 3) has proven to be quite useful in the initial evaluation phase of the illness to define the depth of infiltration and the presence of perigastric lymph nodes (Eidt *et al*, 1994; Sackmann *et al*, 1997; Steinbach *et al*, 1999; Nakamura *et al*, 2001; Ruskone-Fourmestraux *et al*, 2001; Caletti *et al*, 2002; Fischbach *et al*, 2002; Fusaroli *et al*, 2002).

In MALT lymphomas, deep infiltration of the gastric wall is associated with a greater risk of lymph-nodal positivity and a smaller chance of response to antibiotics only (Sackmann *et al*, 1997; Steinbach *et al*, 1999; Ruskone-Fourmestraux *et al*, 2001). In some cases, an ultrasound-endoscopic picture can be evocative of a specific type of gastric lymphoma: diffuse and superficial infiltration is more often indicative of a MALT lymphoma, while the presence of masses is more frequently associated with an aggressive-type histology (Taal *et al*, 1996).

The usefulness of a positron emission tomography (PET) scan has been documented only for DLBC lymphomas (whatever their site) but is controversial for MALT lymphomas, which are frequently reported as PET-negative due to their indolent behaviour (Hoffmann *et al*, 1999; Elstrom *et al*, 2003). The lack of fluorodeoxyglucose (FDG) uptake may also be due to limited tumour volume, as gastric MALT lymphomas can often present with multi-focal, small foci (Wotherspoon *et al*, 1992). The background of the physiological gastric FDG uptake, which appears to be higher in the proximal stomach (Koga *et al*, 2003), may also lessen the accuracy of PET scans at this site. Nevertheless, in a recent study at the Memorial Sloan-Kettering Cancer Center in New York (Beal *et al*, 2005), 60% (6 of 10) of PET-studied gastric MALT lymphomas had positive FDG uptake. In another recent study of 15 patients, the PET scan was positive in all cases of gastric MALT and non-MALT NHL with known active disease, while no pathological ¹⁸F-FDG uptake was evident in the subjects who were in complete clinical remission. The degree of FDG uptake (mean maximum standard uptake values) in MALT lymphomas was, however, much less evident in comparison with aggressive gastric NHL (Ambrosini *et al*, 2006). Kumar *et al* (2004) also reported that a positive PET scan on completion of chemotherapy is a strong predictor of relapse, suggesting that a PET scan can be useful in monitoring the response to treatment in patients with gastro-intestinal tract lymphomas.

In DLBC NHL, accurate staging has immediate therapeutic implications because, should the disease go beyond the stomach and regional nodes, treatment strategies can no longer be focused on local control; rather, systemic, aggressive chemotherapy becomes mandatory.

An otorhinolaryngoiatric examination is recommended in order to exclude involvement of Waldeyer ring, which is occasionally associated with gastric NHL (Zucca *et al*, 1997; Bertoni *et al*, 2000).

Regardless of histology, initial evaluation also calls for the evaluation of lactate dehydrogenase (LDH) and beta-2-microglobulin serum levels, as well as bone marrow aspiration and biopsy. Even though the disease tends to remain localised in the stomach, one must always exclude those rare cases of scattered MALT lymphomas with bone marrow infiltration (approximately 10%) that are associated with a more negative prognosis (Zucca *et al*, 2000). Routine lumbar puncture is unnecessary. In general, a spinal tap is recommended only in the staging of patients with an aggressive histology and with clinical signs and symptoms suggestive of CNS disease or with elements associated with a high-risk CNS relapse (advanced disease with a high LDH level or additional extra-nodal sites).

Therapy

General considerations

Historically, therapeutic strategies in gastric lymphomas have been, for a very long while, based on surgery, followed by radiotherapy or postoperative chemotherapy. This approach began to be questioned at the end of the 1980s, when several retrospective studies (Gobbi *et al*, 1990; Maor *et al*, 1990) showed that surgery should not necessarily be considered obligatory in all patients.

In 1991, a prospective study by the Groupe d'Etude des Lymphomes de l'Adult (GELA) showed – in a series of over 700 patients with advanced-stage, aggressive lymphomas who had been treated with intensive chemotherapy only – that survival of a patient subgroup with NHL that had originated primarily at a gastro-intestinal level (approximately 15%) was no different from the other patients (Salles *et al*, 1991). After this study was published, the concept that advanced aggressive gastro-intestinal lymphomas behaved similarly to lymph-nodal ones having a corresponding histology began to gain acceptance, along with the idea that the latter could be treated with chemotherapy alone.

The effectiveness of chemotherapy alone in advanced stages then brought about a critical revision of the surgical role in localised stages as well (Coiffier & Salles, 1997; Koch *et al*, 2001b). At the same time, the demonstration of the effectiveness of antibiotics in localised MALT lymphomas gave a further push towards abandoning front-line surgery, even for lymphomas with a low-grade malignancy histology, where surgery (with or without 'adjuvant' radiotherapy or chemotherapy) was considered the gold standard (Zucca *et al*, 2002).

Table II. Staging systems for gastrointestinal NHL are still controversial. Called 'Lugano staging', modifications of Blackledge's classification regarding the staging of primary lymphomas of the gastrointestinal tract were proposed in 1993 during the fifth International Conference on Malignant Lymphoma (Rohatiner *et al*, 1994). This Table compares differences and similarities among the classifications most used over the years.

Lymphoma extension	TNM modifications in the Paris system (Ruskone-Fourmestreaux <i>et al</i> , 2003)	Adapted TNM staging system (Steinbach <i>et al</i> , 1999)	Musshof staging (Musshoff, 1977)	Modified Blackledge system (Lugano staging) (Rohatiner <i>et al</i> , 1994)
Mucosa	T1m N0 M0	T1 N0 M0	I _{E1}	Stage I = confined to GI tract (single primary or multiple, non-contiguous)
Sub-mucosa	T1sm N0 M0			
Muscularis propria serosa	T2 N0 M0 T3 N0 M0 T1-3 N1 M0	T2 N0 M0 T3 N0 M0 T1-3 N1 M0	I _{E2} II _{E1}	Stage II = extending into abdomen (Stage II ₁ = local nodal involvement; Stage II ₂ = distant nodal involvement)
Perigastric lymph nodes				
More distant regional nodes	T1-3 N2 M0	T1-3 N2 M0	II _{E2}	
Extra-abdominal nodes	T1-3 N3 M0			
Invasion of adjacent tissues		T4 N0 M0	I _E	Stage II _E = penetration of serosa to involving adjacent organs or tissues
Lymph nodes on both sides of the diaphragm, and/or additional extra-nodal sites with non-continuous involvement of separate GI site	T1-4 N3 M0	T1-4 N3 M0	III _E	
Or non-continuous involvement of non-GI sites	T1-4 N0-3 M1 T1-4NO-3 M2	T1-4 N0-3 M1	IV _E	Stage IV = disseminated extra-nodal involvement or concomitant supra-diaphragmatic nodal involvement
Bone marrow not assessed	T1-4 N0-3 M0-2 BX			
Bone marrow not involved	T1-4 N0-3 M0-2 B0			
Bone marrow involvement	T1-4 N0-3 M2 B1			

NHL, non-Hodgkin lymphomas; TNM, tumour-node-metastasis classification system; GI, gastrointestinal.

It is worthwhile remembering here that, if surgery has been almost completely abandoned in the treatment of gastric localisations, it nevertheless continues to play a crucial role in the diagnosis and treatment of lymphomas with a primary onset in the intestines (Zucca *et al*, 1997; Gobbi *et al*, 2000).

Treatment of early-stage, HP-positive, MALT-type gastric lymphomas

Mucosa-associated lymphoid tissue-type gastric lymphomas have an 'indolent' clinical-biological behaviour pattern, with a tendency to remain localised at the onset site in 70–80% of cases (Cogliatti *et al*, 1991; Radaszkiewicz *et al*, 1992).

At present, the most widely accepted initial therapy for localised disease is aimed at the eradication of HPI using regimens combining antibiotics and proton-pump inhibitors. (One of the most commonly used regimens combines Omeprazole with Clarithromycin and Amoxicillin for 10 d.) Nonetheless, there is no existing data in favour of any of these different schemes (Malfertheiner *et al*, 1997; Howden & Hunt, 1998); consequently, the choice of a treatment regime must take into account the local epidemiology of the infection and the possible resistance to certain antibiotics. This therapeutic approach is the one that is mostly investigated and successfully verified in a large number of clinical studies (Zucca & Cavalli, 2004). Numerous reports have confirmed the effectiveness of antibiotic therapy, substantiating long-term remissions in 60–100% of patients with localised, HP-positive, MALT lymphomas (Wotherspoon *et al*, 1993; Bayerdorffer *et al*, 1995; Roggero *et al*, 1995; Neubauer *et al*, 1997; Pinotti *et al*, 1997; Sackmann *et al*, 1997; Steinbach *et al*, 1999; Nakamura *et al*, 2001; Ruskone-Fourmestraux *et al*, 2001; Bertoni *et al*, 2002). The length of time necessary to obtain complete remission varied from 3 months to more than a year (Zucca & Cavalli, 2004).

There is no evidence whatsoever to justify additional treatment with chemotherapy in patients who respond to antibiotic therapy (Levy *et al*, 2002; Hancock *et al*, 2005). However, evaluation of residual lymphomatous infiltration in gastric post-therapy biopsies can be quite difficult, and there is no uniform criteria in the literature to define histological remission (Bertoni & Zucca, 2005).

Wotherspoon index (Table III), has been proposed to evaluate therapy response (Wotherspoon *et al*, 1993), but it seems to be particularly useful in an initial diagnostic evaluation.

The absence of standardised and easily reproducible criteria makes it quite difficult to compare results presented in various clinical series. A new, post-treatment histological evaluation system was proposed by GELA (Copie-Bergman *et al*, 2003), aimed at providing significant information to clinicians (Table IV). This system seems to offer simple, faithfully reproducible criteria to define clinical results (Copie-Bergman *et al*, 2005). Confirmation of the reproducibility of this evaluation system could make it a useful instrument in the monitoring of the diagnostic-therapeutic course of gastric lymphomas (Copie-Bergman *et al*, 2005).

Using molecular biology techniques, it has been demonstrated that, following antibiotic therapy, there is a persistence of a B-cell monoclonal population in approximately half the patients with gastric MALT lymphomas in complete histological and endoscopic remission. Thus, it is clearly impossible to speak of 'being cured' (Thiede *et al*, 2001; Bertoni *et al*, 2002; Wotherspoon & Savio, 2004). Nevertheless, the clinical significance of this minimal residual disease has not been completely explained. In general, after antibiotic therapy, the presence of disease residue without HP re-infection appears to be a self-limiting phenomenon that is not necessarily associated with a tumour's clinical progression (Isacson *et al*,

Table III. Wotherspoon's histological index (Wotherspoon *et al*, 1993) for the diagnosis and post-treatment evaluation of gastric MALT-type lymphomas.

Wotherspoon index	Definition	Histological characteristics
0	Normal mucous membrane	Occasional plasmacytes in the lamina propria
1	Active chronic gastritis	Small lymphocytic aggregates in the lamina propria, without lymphoid follicles or lymphoepithelial lesions
2	Active chronic gastritis with lymphoid follicles	Prominent lymphoid follicles surrounded by a mantle zone and plasmacytes, without lymphoepithelial lesions
3	Suspected lymphoid in-filtration, probably reactive	Lymphoid follicles surrounded by small lymphocytes that widely infiltrate the lamina propria and, occasionally, the epithelium
4	Suspected lymphoid in-filtration, probably lymphoma	Lymphoid follicles surrounded by centrocytic-like cells that widely infiltrate the lamina propria and the epithelium
5	MALT lymphoma	Dense and widespread infiltration of centrocytic-like cells in the lamina propria, with prominent lymphoepithelial lesions

Treatment response	Definition	Histological characteristics
CR	Complete histological remission	Normal or empty lamina propria and/or fibrosis with absent or sparse plasmacytes and lymphoid cells in the lamina propria without lymphoepithelial lesions
pMRD	Probable minimal residual	Empty lamina propria and/or fibrosis with disease aggregates or lymphocyte nodules in the lamina propria, in the muscularis mucosae and/or in the sub-mucosa
rRD	Residual disease in regression	Lamina propria focally empty and/or fibrosis; dense, diffuse or nodular-infiltrated lymphoid which extends around the glands in the lamina propria. Focal or absent lymphoepithelial lesions
NC	No change	Lymphocytic infiltration dense, diffuse or nodular, with lymphoepithelial lesions (which can also be absent)

Table IV. Histological evaluation system, proposed by GELA, to evaluate MALT-type gastric lymphomas following antibiotic therapy (Copie-Bergman *et al*, 2003).

1999; Bertoni & Zucca, 2005). Notwithstanding the problems related to reproducibility, as mentioned earlier, evaluation with serial biopsies remains the cornerstone follow-up procedure for these patients (Bertoni & Zucca, 2005).

Treatment of patients with advanced or HP-negative, MALT-type gastric lymphomas.

There are no definitive therapeutic guidelines for those patients in whom antibiotic therapy has failed or for those who did not present HPI at diagnosis.

Although different therapeutic procedures have been studied, there are, as yet, no randomised studies that would enable evidence-based decision-making. In two retrospective series of patients with low-grade MALT lymphomas, no significant differences in survival were demonstrated among the various therapeutic procedures followed (Pinotti *et al*, 1997; Thieblemont *et al*, 2003).

In general, gastric MALT lymphomas that are HPI-negative do not regress when treated with antibiotics (Steinbach *et al*, 1999; Ruskone-Fourmestreaux *et al*, 2001) but some response has been reported in early-stage cases (Raderer *et al*, 2006). Therefore, due to the indolent nature of the disease – and before taking into account more aggressive approaches used in antibiotic-refractory patients – an initial therapeutic attempt with antibiotics and proton pump inhibitors might also be considered for HP-negative patients with MALT lymphomas confined to the stomach.

Excellent results in local-disease control have been reported by different groups using radiotherapy on the stomach and perigastric lymph nodes. In particular, Tsang *et al* (2003) reported that up to 90% of patients receiving radiotherapy alone achieved a complete response, with 5-year disease-free and overall survival rates of 98% and 77% respectively. ‘Involved-field’ irradiation (total dose of 30 Gy administered

over 4 weeks) has thus become the therapy of choice for patients with stage I and stage II MALT lymphomas without an HPI or with persistent lymphomas following antibiotic therapy (Schechter *et al*, 1998; Yahalom, 2001; Tsang *et al*, 2003; Gospodarowicz & Tsang, 2004).

The most frequent side-effects of radiotherapy include anorexia, nausea and vomiting. With a dose of 30–35 Gy, no delayed toxicity (such as gastric ulcers or gastro-intestinal haemorrhaging) has been reported, even though long-term effects of radiotherapy on the functionality and integrity of the gastric mucous membrane have yet to be defined (Coia *et al*, 1995; Gospodarowicz & Tsang, 2004).

Historically, surgery has been used as the initial treatment in cases of gastric lymphomas, even those with low-grade malignancy (Cogliatti *et al*, 1991; Bertoni & Zucca, 2005). Nevertheless, there is now sufficient data to demonstrate that conservative therapy permits a better quality of life, with no negative impact on survival rates. Surgery, therefore, no longer assumes a central role in therapeutic strategy and is reserved only for carefully chosen cases in which alternative treatments are not possible (Coiffier & Salles, 1997; Koch *et al*, 2005). Surgery is also limited to the treatment of complications, such as perforation, haemorrhage or obstruction, which cannot be managed conservatively (Koch *et al*, 2001a,b, 2005).

In all patients with disease that has spread, systemic therapy similar to that for other indolent, advanced lymphomas must be taken into consideration (Bertoni & Zucca, 2005). Treatment options include chemotherapy and the use of monoclonal antibodies.

Different cytotoxic agents have been studied, both alone and in combination. Oral alkylating agents (Cyclophosphamide or Chlorambucil) can be effective in most cases (Hammel *et al*, 1995; Levy *et al*, 2002). Other phase II studies have shown the anti-tumoural activity of purine analogues (Fludarabine and Cladribine), though they could be associated with a risk of

secondary, myelodysplastic syndromes (Jager *et al*, 2002, 2004). Alkylating agents or purine analogues induce a complete response in approximately three-quarters of patients with disseminated MALT lymphomas (Hammel *et al*, 1995; Thieblemont, 2005). Interesting response rates have also been reported with Oxalyplatin (Raderer *et al*, 2005). Long-term follow-up data have been recently reported for a group of 19 patients following Cladribine treatment for gastric MALT lymphomas and showed a 6-year, disease-free survival rate of 78% (Jager *et al*, 2006).

Given the indolent course of gastric MALT lymphomas, the need for aggressive combination regimens remains controversial. The combination of Chlorambucil, Mitoxantrone and Prednisone as well as the classic CVP (Cyclophosphamide, Vincristine and Prednisone) have been reported to be active and well-tolerated regimens (Wohrer *et al*, 2003; Zinzani *et al*, 2004); Fludarabine in combination with Mitoxantrone has also been found to be extremely active in a phase II study (Zinzani *et al*, 2004). Aggressive anthracycline-containing regimens are usually reserved for patients with histological transformations or with bulky masses (Thieblemont, 2005).

The use of Rituximab, the anti-CD20 monoclonal antibody (MoAb), has been shown to be effective in therapies for MALT-type, marginal zone lymphomas, with response rates of approximately 70%. This represents a new therapy option for the advanced disease (Conconi *et al*, 2003; Martinelli *et al*, 2005). The combination of Rituximab and chemotherapy in the treatment of MALT lymphomas is presently under evaluation in a clinical trial by the International Extranodal Lymphoma Study Group (IELSG).

Given the molecular pathogenesis of MALT NHL (strictly correlated to the activation of the NF κ B signalling pathway), a group of potentially useful drugs can be found in proteasome inhibitors, Bortezomib being one example (Bertoni & Zucca, 2005; O'Connor *et al*, 2005); but available data are quite limited. In a phase II study of relapsing indolent lymphomas, two marginal zone lymphoma patients were included, and both achieved partial remission lasting 8+ and 11+ months respectively (O'Connor *et al*, 2005). A phase II study conducted by IELSG is currently evaluating the specific activity of Bortezomib in MALT lymphomas.

Treatment of high-grade gastric lymphomas

Diffuse large B-cell NHL represents the most common histological type of gastric lymphomas (Table I). Recent molecular biology data coming from gene-expression analyses suggest that this histotype includes diverse entities which, though morphologically similar, have different aetiopathogenetic and prognostic behaviour patterns (Alizadeh *et al*, 2000).

Treatment of a diffuse large-cell B lymphoma of the stomach is based on aggressive poly-chemotherapy that, today, is usually combined with Rituximab. Scientific support for these

regimens comes from clinical studies carried out mainly on nodal, diffuse large B-cell NHL. These studies have shown a significant improvement in overall survival rates (Coiffier *et al*, 2002).

As previously discussed, surgery has been widely used in the past for diagnostic and therapeutic purposes in those patients with localised disease. However, thanks to the development of ultrasound-endoscopy and CT scans, the need for surgery for those purposes has completely disappeared. Moreover, the assumption of an increased risk of perforation and bleeding with chemotherapy (for which 'debulking surgery' was carried out preventatively) has not been confirmed in any modern series.

In contrast, several studies have reported a high degree of postsurgical complications that resulted in a delay in the start of chemotherapy (Gobbi *et al*, 1990, 2000; Ferreri *et al*, 1999; Popescu *et al*, 1999; Schmidt *et al*, 2004; Koch *et al*, 2005). In the light of such evidence, therapy for diffuse large B-cell gastric lymphomas has changed: systematic, surgical resection has been abandoned for a more conservative approach (Raderer *et al*, 2000, 2002; Koch *et al*, 2001b, 2005; Aviles *et al*, 2004; Yoon *et al*, 2004).

In our opinion, the same guidelines followed for nodal aggressive lymphomas can also be applied to gastric lymphomas with aggressive histologies. For localised stages (stages I and II, I-II in the Lugano Classification), these guidelines suggest front-line chemo-immunotherapy with three to four cycles of standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) followed by 'involved-field' radiotherapy. Radiotherapy toxicity can be reduced by using conformational techniques to minimise doses to the liver and kidneys (Wirth *et al*, 1999; Tsang *et al*, 2003; Gospodarowicz & Tsang, 2004). Advanced-stage patients (stage IV in the Lugano Classification) usually undergo only 6–8 cycles of R-CHOP in order to obtain a complete remission rate similar to their nodal counterparts. Dose-dense regimens, such as CHOP-14 or third line regimens, such as proMACE-cytaBOM (prednisone, methotrexate, adriamycin, cyclophosphamide, etoposide, cytarabine, bleomycin, oncovin, methotrexate) or MACOP-B (methotrexate, adriamycin, cyclophosphamide, oncovin, prednisone, bleomycin), could also be used, but generally with no differences in terms of complete remission induction and 5-year survival expectations (Fisher *et al*, 1993).

Several recent studies have demonstrated possible regression (analogous to MALT lymphomas) even in DLBC localised lymphomas following anti-HP therapy (Montalban *et al*, 2001; Morgner *et al*, 2001; Chen *et al*, 2005); this suggests that an antigenic-drive may remain present in a subset of aggressive gastric lymphomas, though antibiotics could be added to chemotherapy at the clinician's discretion. Nevertheless, before antibiotic therapy alone can be considered 'standard' in the treatment of a diffuse large B-cell gastric lymphoma, these results must be validated by prospective, wider-scale studies.

New therapeutic strategies

Radio-immunotherapy (RIT). Considering the indolent nature of MALT disease and the lack of significant differences in outcome reported among patients treated with different combinations of surgery, radiotherapy and chemotherapy, new therapeutic options – less toxic or more patient-friendly – have been proposed.

As previously reported, Rituximab has been shown convincingly to be effective in treating gastric and extra-gastric MALT NHL, though it has rarely obtained lasting responses when used as a single agent (Conconi *et al*, 2003; Martinelli *et al*, 2005). The synergistic effect of the combination of Rituximab with chemotherapy has been seen in large-cell lymphomas and is being tested in the MALT-types. The development of a radio-conjugated MoAb could also possibly lead to a role for RIT in the management of gastric lymphomas.

Radio-immunotherapy is a new therapeutic option combining immunological and radiobiological mechanisms in which the MoAb activity is boosted by the toxic effect of radiation delivered directly to the tumour site (Cheson, 2003). Meanwhile, cells not directly targeted by the MoAb but close to it may receive a radiation dose as a result of the so-called 'cross-fire effect'. Moreover, ^{90}Y , which is a pure beta-emitter, penetrates tissues up to 11 mm (with a median range of 5 mm), allowing the sparing of undesirable toxicity yet maintaining efficacy. RIT works in a similar fashion to local radiotherapy but avoids the traditional side effects of conventional external beam irradiation (Witzig *et al*, 2001). These characteristics make such an option quite promising in treating diseases requiring a combination of systemic and local therapeutical effects.

Zevalin is a new compound that includes ibritumomab, a murine parent of the humanised anti-CD20 MoAb Rituximab, conjugated by tiuxetan to ^{90}Y . It has been demonstrated to be active in follicular and diffuse large B-cell NHL as well as in cases resistant or refractory to Rituximab (Witzig *et al*, 2002; Morschhauser *et al*, 2004). In particular, two studies recently reported data on efficacy and tolerability of Zevalin in gastric lymphoma patients previously treated with antibiotics, chemotherapy and immunotherapy (Witzig *et al*, 2001; Ferrucci *et al*, 2006). However, further studies are required to define its role in patients with gastric MALT NHL who have relapsed or are resistant to conventional therapies.

Follow-up

Regular follow-up after antibiotics is mandatory because diagnostic gastric biopsies cannot exclude entirely the presence of a concomitant, aggressive, diffuse large B-cell lymphoma, which would require proactive therapy with curative intent. In our institutions, we perform a breath test at approximately 2 months post-treatment to document successful HPI eradication. An (echo)endoscopic examination with multiple biop-

sies should be done 3–6 months after HPI eradication to evaluate lymphoma regression, repeated every 6 months for 2 years and then yearly, to monitor histological remission.

Endoscopic ultrasound is very useful in initial staging and if there are suspicions of a relapse; but it could also provide important information during follow-up.

For aggressive histologies, regular clinical evaluation and repeat blood counts and haematochemistry are scheduled, together with a CT scan every 3–4 months for 2 years and every 6 months for 3 years thereafter. When performed and shown positive at diagnosis, a PET scan should be repeated until there is evidence of complete remission or relapse.

Conclusions

In conclusion, the therapeutic approach for patients with gastric NHL has changed radically over the last 10–15 years, with the abandonment of 'routine' gastrectomies in favour of more conservative therapies. Nonetheless, treatment for primary gastric lymphomas is still controversial.

The general consensus is nowadays limited to using an antibiotic therapy for the initial treatment of MALT-type, HP-positive lymphomas. In all other situations, the choice between local-therapy options (radiotherapy or surgery) and systemic ones (chemotherapy and immunotherapy) must be based on the characteristics of each individual patient (histological type, stage, age, co-morbidities and willingness to undergo a rigorous endoscopic 'follow-up').

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