What you always wanted to know about gastric MALT-lymphoma: a focus on recent developments

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Abstract: The stomach is the most common site of origin for extranodal lymphomas, with extranodal marginal zone B-cell of the mucosa associated lymphoid tissue (MALT-lymphoma) being the predominant subtype. MALT-lymphoma develops in mucosa associated lymphoid structures acquired by infection or chronic antigenic stimuli and may therefore arise in almost any organ of the human body. In spite of histopathologic similarities between various organs upon first glance, recent findings suggest pronounced differences between different sites, with a variety of features specific to gastric MALT-lymphoma. The objective of this review is to sum up the current knowledge on pathogenesis, molecular pathology, clinical presentation and therapeutic approaches to gastric MALT-lymphoma with in-depth discussion of recent developments.

Introduction

Extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma) was originally described by pathologists Peter Isaacson and Dennis Wright, who noted that the pattern of a certain type of gastric B-cell lymphoma was more reminiscent of the structure of the Peyer's patch rather than lymph node architecture.[1] That the stomach became the archetypical organ for MALT-lymphoma was slightly puzzling, as, opposed to the intestine, which includes the largest accumulation of lymphoid tissue in the human body, the stomach is *a priori* not a lymphoid organ. In terms of lymphoma development, however, the roles are reversed, as the stomach is the main organ of extranodal lymphoma development, while it is exceedingly rare in the small bowel.[2] Due to the relatively sterile gastric environment, the association between *Helicobacter pylori* (*H. pylori*) infection and gastric MALT-lymphoma was rapidly discovered.[3] Initially based on epidemiological findings, the process of acquisition of MALT in the stomach by chronic antigenic stimulation leading to clonal expansion of B-cells co-driven

by autoreactive T-cell and cytokines was subsequently delineated.[4] More recent results have further delineated inflammatory changes including production of a proliferation inducing ligand (APRIL), a member of the tumour-necrosis factor (TNF)-family, by macrophages as a result of interaction with *H. pylori*-specific T-cells as contributory to MALT-lymphoma development.[5] A role of T-regulatory cells (T-regs) has also been assessed; the persistence of small compartments including T-regs within the mucosa has been associated with lymphoma development,[6] as has the number of FOX-P3 positive T-regs with response to antibiotics.[7]

In 1993, a pilot series of 6 patients with gastric MALT-lymphoma treated by sole *H. pylori* eradication was published, 5 of whom achieved a complete response.[8] The rest, as they say, is history, as these data by Wotherspoon and Isaacson have revolutionised the therapy of gastric MALT-lymphoma; antibiotic eradication has become the standard first line therapy in such patients. In the 2011 consensus paper, the European Gastrointestinal Lymphoma Study Group (EGILS)

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stated *H. pylori* eradication as the gold standard irrespective of stage in *H. pylori* positive patients.[9] Ironically, most members of the group declared gastric MALT-lymphoma as a vanishing disease anyway, with little potential for further research and more or less closed the chapter (and subsequently also the work as a group).

While the incidence has indeed changed (with the stomach amounting to roughly 30% of site of origin of MALT-lymphomas as opposed to more than 50% in earlier time-periods), in recent years there has been a revival of interest in gastric MALT-lymphoma, which is due to the fact that an increased number of *H. pylori* negative patients are being diagnosed.[2,10,11] While the range was 5–10% in the early 2000s, up to 30% of patients in large volume centres are now considered *H. pylori* negative.[12–14] In addition, the advent of immunomodulatory therapies has changed the approach to patients with disseminated disease and with those refractory to or relapsing after *H. pylori* eradication.[15]

Therefore, the objective of this review is to briefly summarise the state of the art in diagnosis and therapy of gastric MALT-lymphoma, as well as to briefly review recent developments in the field of gastric MALT-lymphoma.

Pathological features and presentation: implications for staging

According to current understanding, MALT-lymphoma arises from mature, post-germinal centre B-cells closely related to the plasma cell.[16] As a consequence, a relevant percentage of patients show expression of monoclonal immunoglobulins [i.e. immunoglobulin G (IgG) or IgM in the large majority] not only on the lymphoma cells, but also detectable in the blood by serum electrophoresis or immunofixation.[17] This is sometimes detected before the diagnosis of MALT-lymphoma is established and erroneously interpreted as monoclonal gammopathy of unknown significance (MGUS). Immunohistochemical characteristics, however, are bland; rather, they are characterised by the absence of specific markers apart from pan-B-cell surface markers including CD79 and CD20. MALT-lymphoma is therefore negative for CD23, CD10, cyclin D1 and CD5, with the rare exception of the latter feature, as small series of CD5-positive MALT-lymphomas have been described.[16,18,19] Intermingled plasma cells are part of the malignant clone, as has been shown by genetic analysis of individual patients harbouring

the same translocation t(11;18)(q21,q21), both in the typical MALT-lymphoma cells as well as in the plasma cells.[16,20] The feature of plasmacytic differentiation might be so pronounced that the tumour is purely composed of plasma cells, which sometimes leads to the diagnosis of extramedullary plasmacytoma. As plasma cells are negative for CD20 as opposed to MALT-lymphoma B-cells, plasmacytic differentiation has also been induced by therapy with the anti-CD20 monoclonal antibody rituximab. It has been suggested that this approach leads to clonal selection/escape of CD20-negative plasma cells when used as monotherapy in such patients.[21]

The presence of a certain number of blasts with B-cell phenotype also appears to be a typical feature of gastric MALT-lymphoma and had repeatedly been described in initial reports.[16,18] However, this was not interpreted as the presence of diffuse large B-cell lymphoma; instead, a grading system was developed to deal with the continuum of the varying number of blasts. The initial term 'high grade MALT-lymphoma' of the stomach, which was used when blasts were apparent in abundance and growing in sheets,[22] was abandoned in later classifications, as such composite lymphomas were designated as both extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue with diffuse large B-cell lymphoma (DLBCL) component.[16] This was mostly based on the notion that these might in fact be two distinct types of malignancy arising in the same organ due to similar pathogenic factors. In initial reports, such composite lymphomas were described in up to 30% of patients,[23] while they have dramatically declined in incidence and are virtually absent nowadays. In addition, the number of pure gastric DLBCL patients, which have also been shown to be related to *H. pylori* infection in up to 50% and might be treated with antibiotics alone, has dramatically reduced in incidence.[24,25] More recent results have shown that the majority of those DLBCL-cases are, in fact, transformed from MALT-lymphoma, even if the rate of transformation in the overall cohort of patients with MALT-lymphomas is low, at <5%.[10,26,27] While transformation appears to be a catastrophic event when occurring outside the stomach, it apparently does not affect the prognosis of patients with isolated gastric transformation.[10]

Apart from the pure descriptive pathology, the models for the development of gastric MALT-lymphoma have become more refined in recent years due to molecular analyses and the use of

modern techniques including next generation sequencing (NGS).

Gastric MALT-lymphoma (in fact, all MALT-lymphomas irrespective of origin) is characterised by a distinct homing tendency to other mucosal structures rather than a spread to lymph nodes or bone marrow.[2] Initial clonal analyses on a number of gastrectomy samples by Du et al.[28] showed an intragastric dissemination on the molecular level in almost all cases; this was also extended to the bowel mucosa, even if to a much lesser extent.[29] The homing features were attributed to interaction of alpha4-beta7 integrins with high-endothelial venules in the mucosal structures preferentially expressed in the gastrointestinal (GI)-tract.[2,30] Interestingly, the circulation pattern appears to be distinct for MALT-lymphoma according to the site of origin and probably reflects early embryological priming of various tissues.[31,32]

As a clinical consequence of these pathological properties, staging appears to be important in MALT-lymphoma, as the rate of dissemination to other mucosal organs is higher than initially reported. According to current knowledge, roughly 20–25% of patients with gastric MALT-lymphoma will have (sub)clinical dissemination upon extensive staging, while the risk in patients with extragastric origin is between 40% and 50%.[10,11,13,33–35] Interestingly, secondary dissemination to the stomach is rare; it almost exclusively occurs in patients with pulmonary MALT-lymphoma and to a lesser extent from the GI-tract.[35] As a result, gastroscopy is a recommended staging procedure in all patients with pulmonary and intestinal MALT-lymphoma in the most recent guidelines published by the European Society of Medical Oncology.[36]

Two current developments in this guideline also deserve further mention. Bone marrow biopsy is no longer mandatory upfront in the overall collective of MALT-lymphoma; instead, it is recommended only in special situation in extra gastric MALT-lymphomas. This is based on the low rate of positive results overall, but also on the apparent absence of clinical impact, which will also be discussed in the paragraph on treatment.

A second point to consider is the use of positron emission tomography (PET)/ computed tomography (CT) for staging of this disease, using fludeoxyglucose (18F) (18F-FDG)-PET/CT, which is the standard for staging and response assessment in most types of lymphoma. In contrast, it has been shown to produce variable results in patients with MALT-lymphoma. In general, the sensitivity of 18F-FDG as a lymphoma-seeking tracer is poor in MALT-lymphoma, as only 50–60% of patients with verified lymphoma will have a positive 18F-FDG-PET/CT result.[2,37,38] This is only in part due to the spatial resolution of the method in small, mucosal gastric deposits; it is also the result of the low affinity of glucose-based imaging in this indolent disease. While histological characteristics appear to play a role and patients with plasmacytic differentiation have been reported to have a significantly higher rate of positive 18F-FDG-PET/CT findings,[39] the general consensus is that 18F-FDG-PET/CT is less reliable than in other lymphomas for clinical routine use. It is, however, recommended in the small cohort of patients with clinical suspicion of transformation in order to assess patients for optimal biopsy sites.[36]

An interesting translational approach to the imaging/staging of MALT-lymphoma is the use of homing receptors for clinical imaging using radiolabelled tracers. In an attempt to characterize the expression of somatostatin receptor (SSTR)-expression on MALT-lymphoma cells, Stollberg and co-workers have used immunohistochemistry not only for assessing SSTR-subtypes 1–5, but also for staining of chemokine-receptor 4 (CXCR4) on samples from MALT-lymphoma patients both of gastric and extragastric origin.[40] While these data to some extent confirmed older results suggesting different patterns of SSTR-expression in gastric versus extragastric MALT-lymphomas, the overall rate of expression was low, at a maximum of 50%.[41] Opposed to this, however, 92% of samples expressed relevant amounts of CXCR4. As a result of these findings, the application of gallium-68 (Ga68)-labelled pentixafor for PET/MR targeting CXCR4 has been tested in a pilot series. It found positive imaging of MALT-lymphoma in 33 of 36 patients evaluated, with the potential for imaging of even small lymphoma deposits.[42] The use of 68Ga-Pentixafor-PET/MR has also been demonstrated as a useful tool for imaging of chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL) and might be included into routine imaging of these lymphoma-subtypes in the near future.[43,44]

Molecular characteristics of gastric MALT-lymphoma

One of the major obstacles to the characterisation of gastric MALT-lymphoma was the fact that changes in management of the disease towards a non-surgical approach have resulted in the virtual absence of fresh tissues and the availability of only small amounts of lymphoma-cells from gastric biopsies. Using state of the art methods, however, molecular patterns for MALT-lymphoma are clearly emerging for different localisations.

One of the most striking features of MALT-lymphoma is the absence of a distinct and characteristic genetic hallmark as opposed to follicular lymphoma or MCL.

Even though the t(11;18)(q21;q21) translocation has been described as MALT-lymphoma specific and was initially reported in gastric MALT-lymphoma, only 25–30% of gastric MALT-lymphomas are thought to harbour this translocation resulting in the baculoviral IAP repeat containing 3 (BIRC-3) (API-2)/mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT-1) (BIRC-3) fusion transcript, rendering the cells less prone to apoptosis.[45,46] Interestingly, this genetic aberration appears to be protective against other changes, as it is usually the sole aberration detected. In addition to MALT-lymphoma, pulmonary MALT-lymphomas express this feature in up to 25% of cases, which is again suggestive of a potential relationship as already suggested by clinical features such a secondary spread of MALT-lymphoma from the lung to the stomach.[47] T(11;18) (q21;q21) is almost absent from other localisations such as the ocular adnexa or the salivary glands and the thyroid, which harbour other mutations/aberrations that are characteristic to a certain extent for the localisation, but not the disease of MALT-lymphoma as a whole.

Promotion of the nuclear factor (NF) Kappa (κ) B pathway, however, is thought to constitute a central mechanism in MALT lymphoma irrespective of origin, as a high percentage of genetic changes influencing the NF-kB pathway are commonly detected.[45,48] This includes, apart from the already mentioned t(11;18)(q21;q21)/BIRC3-MALT1, the rarer t(14;18)(q32;q21)/immunoglobulin heavy locus (IGH)-MALT1 and t(1;14)(p22;q32)/ BCL10-IGH. Recently published series using NGS have reported somatic mutations affecting the NF-κB/B-cell receptor (BCR) signalling such as

TNF alpha induced protein 3 (*TNFAIP3*) (*A20*), caspase recruitment domain family member 11 (*CARD11*), CD79b molecule, immunoglobulin-associated beta (*CD79B*) and myeloid differentiation primary response protein (*MYD88*) at site specific, but high incidence.[45,48–50]

The clinical relevance of t(11;18)(q21;q21) has repeatedly been discussed and initial studies have suggested that patients with this alteration are less prone to lymphoma regression after antibiotic eradication of *H. pylori*.[9,51–54] Initial retrospective studies have suggested that t(11;18)(q21;q21) defines about 75% of non-responders to *H. pylori* eradication; recent studies have further underscored the association with impaired response to antibiotics, more disseminated disease and shorter progression free survival (PFS), which was 26% at 10 years as opposed to 57% in negative patients in a large analysis.[55]

Histological assessments have also suggested that t(11;18)(q21;q21) and nuclear BCL10 overexpression are detected at higher numbers in *H. pylori* negative than in *H. pylori* positive gastric MALT lymphoma patients.[52,54] Routine assessment before initiation of therapy is nevertheless not recommended, as also patients testing positive for this translocation might respond to antibiotics, and no influence on response to chemotherapies including cladribine, chlorambucil or bendamustine as well as rituximab has been documented.[56–59]

Treatment of gastric MALT-lymphoma: the Helicobacter enigma

The causal relationship between *H. pylori* gastritis and MALT-lymphoma development has repeatedly been reviewed and has formed the basis for the current standard approach to gastric MALT-lymphoma.[4,60,61] According to current knowledge, patients with *H. pylori* associated gastric MALT-lymphoma should be given antibiotics according to the regional resistance profile of the bacteria, irrespective of stage.[36] About 75–80% of patients will respond to this treatment, although the optimal time to response may take up to 24 months.[2,62,63]

Response assessment should be based on histological assessment of control-biopsies, as imaging using CT; and in addition, endosonography has been shown to be less reliable than pathological evaluation.[9,36] Samples should be evaluated by an experienced hematopathologist according to the

so-called GELA-criteria, which have been developed especially for this situation. The relatively simple scoring system distinguishes between no change (NC), responding residual disease (rRD), probable minimal residual disease (pMRD) and complete remission (CR) and has been shown to be highly reproducible.[64]

The fact that this treatment is effective irrespective of stage (and that bone marrow biopsy might in fact be academic, as already discussed) is illustrated by an analysis recently published by Gong and co-workers.[65] In this study, a total of 496 patients with gastric MALT-lymphoma in whom a bone marrow biopsy had been performed underwent only antibiotic therapy. The rate of bone marrow involvement was 6.7% (33/496), but no significant difference in terms of response rate (RR) between negative (85.7%) *versus* positive patients (78.6%) was found; and no influence of bone marrow involvement on other outcome parameters was detected.

Current guidelines also recommend that patients responding to antibiotic therapy should not receive further therapy.[9,36] This is based on two studies that have evaluated the evolution of gastric MALT-lymphoma after *H. pylori* eradication, even if patients only achieved a partial remission. In a randomised trial published by Hancock and co-workers, the IELSG randomised patients to application of oral chlorambucil *versus* no treatment following successful eradication of *H. pylori*.[66] No significant difference in terms of event-free or overall survival (OS) was demonstrated between the two arms, both for patients with complete as well as partial response to *H. pylori* eradication.

In the second study, a retrospective analysis of 108 patients with minimal residual at a minimum time of 12 months after eradication was performed.[62] At a median follow up of 42 months, only 6 patients progressed, while 67 remained unchanged and 35 went on to achieve a CR with prolonged follow-up.

A recent analysis of 137 patients with gastric MALT-lymphoma (including 96 treated with *H. pylori* eradication only) nevertheless has shown that patients achieving a CR after first line therapy had a significantly longer PFS (96 months) as compared to patients with only partial response (31 months, $p = 0.19$).[13] These data, however, should not be interpreted as to force a complete remission with aggressive therapy in case of only PR, but rather that the response is reflective of a more indolent/responsive lymphoma and that the follow-up intervals (which are usually 3 months after *H. pylori* eradication for two years and then 6 months for 5 years, but lifelong surveillance) could probably be less stringent following CR than PR.

One of the most interesting developments, however, has been the increase in *H. pylori* negative patients with gastric MALT-lymphoma. Initially rated as a rare curiosity at 5–10% of all patients, the rate has been increasing over the last 20 years and now amounts to up 30–50%.[12–14,67] The definition of *H. pylori* negativity, however, has to be taken with some caution, as absence of the gram-negative rods on immunohistochemical staining on biopsies is common with more pronounced *H. pylori*-gastritis and is not untypical in patients with MALT-lymphoma.[9] The pronounced changes in the gastric environment caused by the chronic inflammation and lymphoma development paradoxically leads to withdrawal of the bacteria from the stomach, while the breath test, stool antigen and serology are still positive. It has been hypothesized that *H. pylori* might hibernate in coccoid form or migrate to other sites.[68] By strict definition, *H. pylori* negativity would require absence of bacteria on histology, a negative breath test/stool antigen and negative serology.[69] The problem of *H. pylori* negative gastric MALT-lymphoma has been given only limited attention in the past, as it was thought to be an exceedingly rare phenomenon; patients were immediately treated with radiation or systemic therapy after diagnosis.

Various explanations, including false negative test results, the presence of as yet undisclosed bacteria/infections as causal agents, as well as development of MALT due to autoimmune diseases (AD) have been discussed.[12,14,70] In fact, scattered retrospective data on the *Helicobacter heilmannii* (*H. heilmannii*) infection in patients with gastric MALT-lymphoma with subsequent regression following antibiotics have been published.[71] In addition, a higher than expected rate of chronic autoimmune thyroiditis Hashimoto (HT) was found in an analysis of patients with gastric MALT-lymphoma, and patients with HT showed a significantly lower response rate following antibiotic therapy (7%), even though the numbers were too small to draw meaningful conclusions on the role of autoimmunity in this condition.[72]

A larger series on autoimmunity in patients with MALT-lymphoma found an association with extragastric MALT-lymphoma rather than gastric MALT-lymphoma with autoimmune diseases and a total incidence of 40% of AD, though these data cannot rule out an association in individual cases.[73]

In older studies on antibiotic therapy, scattered patients rated *H. pylori*-negative on the basis of histology had been included in addition to the commonly held belief was that such patients do not benefit from antibiotics. A small retrospective series from our institution, however, including 6 patients with 'state of the art' negative gastric MALT lymphoma treated with eradication cast some doubt on that dogma, as 5 patients responded, with 4 of them even achieving durable CR.[74] This series was later extended to encompass 13 eradicated patients (from a total of 97, 24 of whom were *H.pylori* negative), with 6 responding (5 CR, 1 PR) and 4 had stable disease over a median follow-up of 95 months, suggesting that responses are indeed durable in this cohort of patients, with no difference in estimated time to progression between *H. pylori* negative and positive patients.[67] As opposed to other series, the rate of t(11;18)(q21;q21) was low, with 3/ 13 being positive, one of whom responded (pMRD) and two had stable disease/ no change.

Similar data were subsequently reported mostly from Asia, with RRs of *H. pylori* negative patients between 30% and 50%.[12,75,76] In a review analysing data from various trials including 110 patients, 17 (15.5%) were rated as complete responders.[77] However, a recent meta-analysis found a pooled CR rate of 29.3% [confidence interval (CI) 22.2–37.4%], with patients having t(11;18)(q21;q21) showing a lower RR (19.9%), but also studies that applied serologic testing reported a lower rate of CR (27.5%).[78] Not surprisingly, in studies were non-response was assessed and defined less than 12 months after eradication, also a lower CR rate was reported (27%). This is in analogy to eradication in *H. pylori* positive patients and again questions the current guidelines that such patients should receive alternative therapy if at 6 months no remission is demonstrated,[36] but underscores that patience is indeed a virtue when following the clinical course of gastric MALT-lymphoma, as premature assessment of response might miss late remissions, which are a typical feature of this disease.

The explanation of the success of antibiotics in apparently *H. pylori* negative patients still remained somewhat elusive; again it was hypothesised to be related to undetected bacteria or direct antineoplastic activity of certain antibiotics, especially clarithromycin.[78] This macrolide is in fact a highly active anti-lymphoma agent, as it displays potent immunomodulatory effects leading to high RRs of up to 50% in heavily pre-treated patients with MALT-lymphoma.[79–81] This activity, however, is usually seen with prolonged application, as the generally recommended duration of therapy is 6 months at daily 2×500 mg.[80] In the course of *H. pylori* eradication, clarithromycin is usually given for a maximum of 14 days; some studies even used regimens not including the macrolide.

One of the most likely explanations is the existence of other, not easily detectable bacteria or Helicobacter species. In fact, a number of so called 'non *H. pylori* helicobacter' species that are able to infect humans have been reported, including *helicobacter suis* (*H. suis*), *helicobacter felis* (*H. felis*), *Helicobacter bizzozeronii* (*H. bizzozeronii*), *helicobacter salomnois* (*H. salomnois*) and the already mentioned *H. heilmannii* s.s.[9,70,71,82] As opposed to *H. pylori* and *H. Heilmannii s.s.*, the diagnosis is not always straightforward with the more elusive subtypes, but recent data from Asia using a polymerase chain reaction (PCR)-based approach have revealed a higher than expected rate of infection in *H. pylori* negative patients with gastric MALT-lymphoma.[70] In this pilot series, coinfection with *H. pylori* was found in 10% of patients, but gastric MALT-lymphoma rated negative for *H. pylori* had a positive PCR for non-*H. pylori*-helicobacter species in 55%. The CR-rate was significantly higher in patients with non-*H. pylori*-helicobacter-infections at 75%, while it was only 23% ($p < 0.05$) in true negative cases. These data suggest that these infections are a contributing factor to successful eradication in such patients.

In a relevant percentage, however, the effect of antibiotics remains elusive to date; as a result, all patients with gastric MALT-lymphoma should be given a chance at sole antibiotic treatment for upfront management.

The role of *H. pylori* in the development of gastric MALT-lymphoma nevertheless also has additional implications, as the gram-negative rod has also been defined as class I carcinogen for the

development of gastric cancer. As a consequence, patients with gastric MALT-lymphoma have repeatedly been reported to be at higher risk for metachronous gastric cancer.[83] In fact, precancerous lesions, i.e. intestinal metaplasia have been reported to occur in 50–68% of patients with gastric MALT-lymphoma, with their onset being 6–18 months after lymphoma diagnosis.[84,85] In view of this, and also due to the fact that patients with MALT-lymphoma are thought to have a substantial risk of relapse even after decades, lifelong follow-up both for gastric lymphoma as well as adenocarcinoma appears justified.

Failing Helicobacter eradication: a brief overview

It has already been stated that patients responding to first line *H. pylori* eradication should not receive further therapy, even in the presence of lymphoma remnants. In patients with relapse after CR, re-eradication might be attempted with the potential for another CR. Depending on the geographical location, such a recurrence might be associated with re-infection, but antibiotics should also be given in the absence of *H. pylori*.[86]

Patients in need of therapy after *H. pylori* eradication may be treated with radiotherapy in case of localised disease but may also be given systemic therapies both for localised as well as disseminated disease.[9,36]

The value of radiotherapy for local control in MALT-lymphoma is well established and has repeatedly been reviewed in the past. Due of the vast experience in many centres, the excellent local control, as well as lower doses being more and more applied, radiotherapy is in fact the preferred method of therapy for localized disease in many centres. One of the most comprehensive retrospective analyses has included 487 patients with both gastric as well as extragastric MALT-lymphomas in stage I/II, including 32% of patients with gastric MALT-lymphoma.[87] Local control was excellent, especially for gastric and thyroid MALT-lymphomas and relapses within the radiation field were almost absent. One of the major points of discussion has been the rate of side effects with radiotherapy in this indolent (and mostly asymptomatic) disease, as in older series higher radiation doses were applied and were often in excess of 30 Gy.[88,89] With lowering the intensity, radiation gastritis and ulcerations have become rare events, while the optimal dose

has been the topic of debates and ongoing trials. The most recent data have been published by Hoskin *et al.*,[90] and have investigated the use of 24 Gy *versus* 2×2 Gy for indolent lymphomas including marginal zone lymphomas in a randomized setting. Designed as a non-inferiority trial, an interim analysis had suggested that 2×2 Gy might be a valid option. The mature data nevertheless clearly show that 24 Gy should be the preferred treatment of choice for long term control, and 2×2 Gy are a valid option if only a palliative approach for local control is necessary.

In the EGILS-consensus statement from 2011, both radiotherapy and chemotherapy were considered to have equally curative potential in localized disease.[9] A plethora of agents have been applied for therapy of MALT-lymphoma, but no clear standard has emerged due to the fact that different localisations had been included in those (mostly small) trials, or MALT-lymphoma had been included in small numbers in a cohort of 'indolent lymphomas'. For discussion, the interested reader is referred to specific review articles.[15,91] In addition, the only randomised study in MALT-lymphoma (IELSG-19) has been performed in patients with disseminated lymphoma.[92] In this trial, patients were initially randomised between oral chlorambucil *versus* rituximab plus chlorambucil, and a third arm with rituximab monotherapy was amended later. Overall, the EFS and RR were significantly higher for the combination arm (EFS 68% *versus* 50% and 51% for the monotherapy arms at 5 years), the OS was not different; as a result, it is difficult to extrapolate this combination as standard for clinical practice.

While the high activity of chemotherapy has been shown with various agents and combinations approaching response rates of 100%, a more recent focus has been on immunomodulatory therapies in view of the pathogenesis of the lymphoma.[15] Apart from the long established use of anti-CD20 antibodies, the IMiD lenalidomide has been studied either as monotherapy or in combination with rituximab.[93,94] The good activity in monotherapy with overall RR of 61% could further be improved by addition of rituximab, with an ORR of 80% with 54% complete responses. Interestingly, and in keeping with the rationale of a long standing immunomodulatory effect of the drugs, responses also were seen late after discontinuation of therapy, with a median time to best response of 7.3 months, but patients

still improving their response 44 months after initiation of therapy.[95] Of interest is the fact that opposed to multiple myeloma, the assessment of cereblon/MUM-1 on lymphoma cells did not show an effect on the expression of these markers on response to lenalidomide-based therapy.[96]

As a result, the recent ESMO guidelines recommend the combination rituximab/lenalidomide (also sometimes referred to as "R²") as a potential treatment option for relapsed/refractory MALT-lymphoma.[36] On a side-note, the problem of including an unselected cohort of marginal zone lymphoma and MALT-lymphomas in a trial of indolent lymphomas as opposed to studies on MALT-lymphoma only is highlighted by data on R² generated within the AUGMENT-trial.[97] The data from this phase III trial comparing R² with rituximab + placebo in indolent lymphoma have led to approval of the combination for all subtypes included in the trial (including marginal zone lymphoma) by the FDA, while the EMA has granted approval only for the subgroup of follicular lymphoma. A *post-hoc* analysis of the marginal zone lymphoma cohort consisting of 63 patients with MALT-lymphoma, splenic and nodal marginal zone lymphoma has shown no difference for PFS between both arms. However, the fact that those mixed cohorts have been included without stratification, imbalances in prognostic factors are present between the two arms, which in fact could have heavily biased the results in favour of the R + placebo – arm.

The potential role of the macrolide clarithromycin as a direct antineoplastic agent has been well established in MALT-lymphoma, with apparently better activity in gastric as opposed to extragastric MALT-lymphoma.[15,79,80] The recommended dose is 2 × 500 mg daily for a total of 6 months, and an ORR of 54% (24% CR) and a 52% PFS at 36 months in the overall cohort of MALT-lymphoma is highly promising.[80] Comparable data have also been reported for the BTK-inhibitor ibrutinib, which showed an ORR of 53% and 62% PFS at 18 months in 63 patients with marginal zone lymphoma, nevertheless including only 32 patients with MALT-lymphoma.[98]

No randomised trials have been performed in MALT-lymphoma to assess whether chemotherapy or immunotherapy are more favourable following *H. pylori* eradication. A recent retrospective analysis from our institution has nevertheless suggested that even though the response rate might be higher for therapies including chemotherapy (90% *versus* 68%, with CR rates of 75% *versus* 43%), there was no significant difference in terms of PFS (81 *versus* 76 months), making immunotherapy an attractive and well tolerated option.[99]

Conclusion

The pathogenetic insight into the development of gastric MALT-lymphoma has not only led to its definition as the archetype of an antigen-driven malignancy but have also revolutionised the therapeutic approach to this disease. Antibiotic therapy is the mainstay of management irrespective of stage and interestingly to some extent also to the presence of *H. pylori*. The advent of immunotherapeutic therapy might form the backbone of the future state-of-the-art in case of non-response to antibiotics.

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