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Position Paper

Gastrointestinal lymphomas: French Intergroup clinical practice recommendations for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFH)☆

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ABSTRACT

Introduction: This document is a summary of the French Intergroup guidelines on the management of gastro-intestinal lymphomas, available on the web-site of the French Society of Gastroenterology, SNFGE (www.tncd.org), updated in September 2017.
Methods: This collaborative work was realised under the auspices of several French medical societies and involved clinicians with specific expertise in the field of gastrointestinal lymphomas, including gastroenterologists, haematologists, pathologists, and radiation oncologist, representing the major French or European clinical trial groups. It summarises their consensus on the management of gastrointestinal lymphomas, based on the recent literature data, previous published guidelines and the expert opinions.
Results: The clinical management, and especially the therapeutic strategies of the gastro-intestinal lymphomas are specific to their histological subtypes and to their locations in the digestive tract, with the particularity of gastric MALT lymphomas which are the most frequent and usually related to gastritis induced by *Helicobacter pylori*.
Conclusion: Lymphomas are much less common than epithelial tumours of gastro-intestinal digestive tract. Their different histological subtypes determine their management and prognosis. Each individual case should be discussed within the expert multidisciplinary team.

1. Introduction

Primary gastro-intestinal lymphomas (PGIL) are non-Hodgkin lymphomas (NHL) derived from MALT (Mucosa Associated Lymphoid Tissue) [1]. PGIL are rare, corresponding to 1% of all gastro-intestinal tumours. Their incidence varies among different countries between 0.58 and 1.31/100,000 inhabitants and the usual age of diagnosis is between 50 and 70 years [2,3]. Stomach is the most frequent site of these lymphomas, followed by the small intestine and the colon [4]. Both B and T lymphocytes may give rise to PGIL, but B-cell lymphomas are much more frequent (90%) than T-cell lymphomas (10%.)

PGIL comprise different clinico-pathological entities which should be distinguished since their cellular origins and clinical presentations determine their evolution and treatment. Rare prospective studies taking into account the recent classifications and proposing standardised treatments [4–6], improved our knowledge on these lymphomas. Although gastro-intestinal locations represent 36% of the extra-nodal forms of NHL, these tumours remain rare, which, together with the great diversity of their anatomo-clinical forms and their sometimes slow progression, explain the difficulty of developing randomised therapeutic trials

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specific to the digestive localisations. In consequence, the indication of chemotherapy in the chemo-sensitive forms comes mainly from randomised studies performed in nodal NHL which are much more frequent. The recent recommendations, like those published by the European Gastro-Intestinal Lymphoma Study Group (EGILS) [7] or by the European Society for Medical Oncology (ESMO) [8,9], concern essentially gastric lymphomas and derive mainly from the results of small series or expert opinions.

The clinical management of the PGIL, and particularly the therapeutic strategies, are specific to their histological types and to their location in the digestive tract, with the particularity of gastric MALT lymphomas which are the most frequent and usually related to *Helicobacter pylori (H. pylori)* — induced gastritis.

2. Methodology

This collaborative work was realised under the auspices of several French medical societies and involved clinicians with specific expertise in the field of gastrointestinal lymphomas, including gastroenterologists, haematologists, pathologists, and radiation oncologist, representing the major French or European lymphoma study groups. It summarises their consensus on the management of gastrointestinal lymphomas, based on the recent literature data (original publications, prospective non randomised studies, reviews), previous published guidelines and the expert opinions [7,8]. The recommendations outlined below do not generally fulfil the criteria for high level evidence since no prospective randomised trials are available in the field of this rare disease. The two levels of recommendations, designed as "recommendations" or "options", are mainly based on expert opinions.

3. Diagnosis

The diagnosis of lymphoma is based on histology and should be always confirmed by an expert pathologist [7]. In France, a second histological analysis by an expert pathologist belonging to the national group of expert pathologists for lymphomas (LYMPHOPATH), is mandatory for all types of lymphomas.

For histological diagnosis, several biopsies must be obtained (10–20) from the tumour area and additionally from the normally looking antral and corpus mucosa (for the assessment of the presence of *H. pylori* and associated lesions, like atrophy and intestinal metaplasia). The biopsies are fixed in formalin for histological, immuno-histochemical and molecular analysis. Frozen biopsies are not necessary for routine diagnosis but can be recommended for clinical research. More rarely, the diagnosis is made during emergency surgery performed for complications, like haemorrhage or obstruction (especially for lymphomas located in the small intestine) [10].

For gastric forms, testing for *H. pylori* is mandatory. The method of choice is histology, based on the assessment of biopsies taken from the antrum and from the body, away from mucosal lesions, performed using Giemsa or cresyl violet staining, and if necessary, completed by immuno-histochemistry with anti-*H. pylori* antibodies. In case of negative histology, serology is recommended, and this is the only indirect diagnostic test not affected by proton pump inhibitor (PPI) or antibiotic treatment. The ^{13}C-labelled urea breath test is useful for confirming the eradication of bacteria after the treatment. Moreover, the molecular methods, and in particular a real-time PCR may be used for *H. pylori* detection. This method has excellent sensitivity and specificity, it also allows the detection of mutations associated with macrolides resistance, and it does not require specific conditions for the transport of the biopsies. However, there have been no larger studies testing PCR in patients with MALT lymphoma but only some case reports have been reported [11].

The *H. pylori*-positive status is defined as a positive histology and/or a positive serology [12]. It should be noted that histology, ^{13}C-urea breath and culture should be performed after an interval of at least 4 weeks from any antibiotic treatment and at least 2 weeks after stopping the PPI [12,13].

Table 1
Different histopathological types of gastrointestinal lymphomas (according to WHO classification 2016, Ref. [11]).

B Lymphomas
• Extra-nodal marginal zone of the Mucosa Associated Lymphoid Tissue: MALT including alpha Chain Disease (IPSID)
• Diffuse large B-cell
• Mantle cell
• Burkitt
• Follicular
T Lymphomas
•Associated or not with an intestinal-type enteropathy (with or without villous atrophy) of low and especially high grade of malignancy

4. Histomorphological classification

The different types of primary lymphomas of the digestive tract were initially described by Isaacson [1], but currently the latest 2016 WHO classification for all NHL is considered the reference and diagnosis should be given according to this classification [14]. It takes into account the cellular origin of the proliferation, determined according to morphological and immuno-histochemical criteria (Table 1).

The most frequent are B-cell lymphomas (90% of cases), and very rare T-cell lymphomas. The majority of PGIL originate from MALT. In Western countries, gastric lymphomas are the most frequent and they are represented by two major types: extra-nodal marginal zone lymphomas (MZL-MALT, also called MALT lymphomas), corresponding to the proliferation of small B-cells, and diffuse large B-cell lymphomas (DLBCL), composed of large B-cells, usually developed de novo, but sometimes evolving from transformed MALT lymphomas. In the intestine, all the varieties of NHL, similar to the nodal types, can be found.

In extra-nodal gastric MALT lymphomas, after eradication of *H. pylori* and for the follow-up, the histological results are given according to the GELA (Groupe d'Etude des Lymphomes de l'Adulte) histological scoring system [15] (Table 2).

Because of important prognostic and therapeutic implications, the histological sub-type of the lymphoma must be accurately established. The opinion of expert pathologists, reviewing the slides

Table 2
Histological scoring system of GELA for the post-treatment assessment of gastric MALT lymphomas (According to Copie-Bergman et al. [15]) .

Score	Lymphoid infiltrate	LEL	Stroma
CR	Absent or scattered plasma cells and small lymphocytes in LP	Absent	Normal or empty LP and or fibrosis
pMRD	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
rRD	Dense, diffuse or nodular extending around glands in the LP	Focal or absent	Focal empty LP and/or fibrosis
NC	Dense, diffuse or nodular	Present — May be absent	No changes

CR: complete histological remission; pMRD: probable minimal residual disease; rRD: responding residual disease. NC: no change; LP: lamina propria. MM: muscularis mucosa. SM: submucosa. LEL: lymphoepithelial lesions.

and applying complementary techniques, is recommended for all types of lymphomas in order to confirm the diagnosis [7]. Looking for clonality is not mandatory but can be useful in case of difficult diagnosis. Searching for a (11;18) translocation in MZL-MALT is optional, and if possible, may be carried out by the FISH technique on formalin-fixed biopsies [9] since it may be predictive of response to treatment. Indeed, it has been shown that the presence of this translocation in tumour cells is associated with the non-regression of lymphoma after eradication of *H. pylori* [16] and with a lower response rate to chemotherapy [17].

5. Pre-treatment workup and staging

Pre-treatment work-up recommendations are based on the experts' agreement [7,9]. Two levels of work-up can be distinguished: the reference level (recommended examinations), usually applied for all types of lymphomas, and the optional level, comprising examinations indicated depending on the type/site of lymphoma and on clinical situation.

5.1. Clinical examination and blood tests

5.1.1. Recommendations

Clinical examination includes the evaluation of WHO general status, the presence of general signs, and the physical examination including the examination of peripheral lymph nodes, liver, spleen, and ENT examination.

Blood tests should include complete blood count, beta-2-microglobulin level, serum protein immunofixation, lactate dehydrogenase (LDH) level, and viral serologies (HIV, hepatitis B and C).

5.1.2. Options

Additionally, and depending on the type of lymphoma, other tests may be performed like *H. pylori* serology (in gastric lymphomas, especially if absence of bacteria in histology) [12], liver tests, uricemia, anti-endomysium and anti-transglutaminase antibodies (for T-cell lymphomas), or a search for a monoclonal lymphoid population in the blood.

5.2. Endoscopic workup

5.2.1. Recommendations

Endoscopic workup includes oesophago-gastro-duodenoscopy and ileo-colonoscopy with systematic biopsies, even in the absence of macroscopic lesions [18]. Endoscopic ultrasound is indicated in gastric lymphoma, since it has a prognostic value at diagnosis and sometimes during a follow-up in the case of medical treatment [19], and may also be proposed for rare localisations in the oesophagus or in the rectum.

5.2.2. Options

Magnetic resonance enterography or even enteroscopy (if small intestine biopsies are necessary for diagnosis), as well as video-capsule endoscopy (rarely useful), may be proposed in case of small intestinal lymphomas [20].

5.3. Other explorations

5.3.1. Recommendations

Abdominal, pelvic and thoracic CT-Scan is mandatory in all types of lymphomas, as well as the CT-Scan and/or endoscopy of the nasal cavity and biopsies if there remains a doubt after the ENT examination or in the presence of ENT symptoms.

5.3.2. Options

Optionally, other explorations may be proposed (of debatable interest or according to the type of lymphoma):

1. Osteomedullary biopsy, systematic for certain types of lymphoma (follicular B lymphomas or mantle B-cell lymphomas), optional for other types (for gastric MALT lymphomas: only if there is no regression after eradication of *H. pylori* and optional for large B-cell lymphomas) [21].
2. FDG-PET to determine the chemosensitivity under treatment by immuno-chemotherapy for diffuse large B-cell lymphomas and follicular lymphomas. This examination is undergoing evaluation in marginal zone MALT lymphomas where it is generally negative. High FDG uptake has nevertheless been found at a lesser degree in MALT lymphomas not responding to *H. pylori* eradication leading to the suspicion of transformation [22].
3. Study of the cerebral spinal fluid (with cytocentrifugation) for lymphomas with a high risk of invasion or relapse in the central nervous system (high grade of malignancy like DLBCL with extensive tumour mass, or Burkitt's histological subtype).
4. Electrocardiogram and study of myocardial function (ventricular ejection fraction or cardiac ultrasound if anthracyclines are considered) as pre-therapeutic procedures for lymphomas with a high grade of malignancy before chemotherapy.

5.4. Clinical stage

Clinical stage is expressed according to the Ann Arbor staging system modified by Musshoff. Most of the primary digestive lymphomas (70% of cases) are localised and correspond to stage IE (involvement of the digestive wall), stage IIE1 (involvement of the peri-tumoral lymph nodes), or stage IIE2 (involvement of distant lymph nodes, with a worse prognosis). Another staging system specific for gastric localisations, explored by endoscopic ultrasound, is the EGILS (European Gastro-Intestinal Lymphoma Study) group staging system, inspired by the TNM classification [23].

Besides the clinical stage, other parameters have been identified in the International Prognostic Index for non-Hodgkin lymphomas. This index determines the prognosis and therapeutic approach for aggressive lymphomas with a high grade of malignancy. It takes into account the patient's age, the WHO general status, the LDH level and the number of extra-nodal sites involved. It can be adapted for the large cell digestive lymphomas and it should be emphasised that the majority of gastric large-cell NHL are classified as having a good prognosis, as they are often localised, developed in the patients with a good WHO general status and a normal LDH level [4,5].

6. Treatment and prognosis

6.1. Gastric B-cell lymphomas

6.1.1. Extra nodal marginal zone MALT lymphomas (with small B-cells, low grade of malignancy)

6.1.1.1. Recommendations. Recommendations come from experts' agreement from EGILS recommendations [7] and ESMO guidelines [8].

Since most of these lymphomas are localised, eradication of *H. pylori* is the first-line treatment of choice for all gastric MALT lymphomas. This treatment is usually indicated for *H. pylori*-positive lymphomas (positive histology and/or serology), but it is also recommended if the *H. pylori* status is negative [24,25]. As for the therapeutic regimen to be used, we can refer to the latest Maastricht consensus which recommends, as the first line of empirical treatment, either a bismuth-based quadruple therapy or concomitant

quadruple therapy [13]. The control endoscopy of the lymphoma has to be performed 6 weeks after the completion of treatment to check the evolution of endoscopic lesions (to make sure that there is no macroscopic progression) and eradication of *H. pylori*. Additionally, a ^{13}C-labelled urea breath test (Helikit®, OrInfai®) should be performed to confirm the eradication of the bacteria.

Endoscopic follow-up of gastric lymphoma, with multiple biopsies on scar zones, should be performed every 6 months for the first two years, then once a year for a duration not defined by guidelines.

The tumour response is assessed both, endoscopically and histologically: scarring of macroscopic lesions and histological regression of the lymphomatous infiltration best evaluated by the GELA histological scoring system [15]. This grading should always be performed in the context of reviewing and comparing to the previous biopsies. It shows a good inter-observer agreement. According to this system, the following types of histological response can be distinguished: (1) complete histological response (CR), corresponding to the complete disappearance of tumour infiltration; (2) probable minimal residual disease (pMRD), corresponding to the persistence of some lymphocytic aggregates in the chorion; (3) responding residual disease (rRD), corresponding to the persistence of infiltration of the chorion by lymphocytes, with no lympho-epithelial lesion, considered as a partial response; (4) no change (NC), corresponding to the absence of change in comparison to the initial biopsies, considered as non-response to treatment.

Complete remission is defined as the absence of macroscopic lesions and negative histology (CR or pMRD) in two subsequent follow-up examinations, partial remission as normalisation or reduction of macroscopic findings with histological rRD, and stable disease as unmodified macroscopic lesions and/or histological NC. Finally, progressive disease is defined by worsening of macroscopic lesions, or lymphoma dissemination, or transformation into DLBCL [7].

The published series reported variable rates of remission according to the modalities of initial workup and clinical stage. The endoscopic ultrasound at diagnosis has a prognostic and predictive value of the lymphoma's response to the eradication of *H. pylori* [18,19,26], but is of little help for follow-up. The chances of complete remission are 80% in case of stage IE (or TN0M0B0, as assessed by endoscopic ultrasound, according to Paris staging system) and *H. pylori*-positive status [19,27,28]. The presence of t(11;18) translocation in the tumour cells is associated with resistance (no regression) of the lymphoma to *H. pylori* eradication [16,29].

The tumour response can be slow, which necessitates a follow-up of up to 24 months after eradication of bacteria (median time of occurrence of remission is 6 months with the extremes from 3 to 24 months). The remission must only be pronounced after at least two successive negative examinations (experts' agreement). In some cases, a microscopic lymphomatous residual disease (in the absence of endoscopic lesions), histologically defined as the presence of some pathologic lymphoid islets, can persist 2 years or even more after bacterial eradication, and its significance is not known [30]. In these cases, the continuation of surveillance should be rather privileged over an active treatment. In all these cases, the new GELA histological grading system may help to better standardise a definition of the remission of lymphoma.

According to the currently available data coming from the long-term 25-year follow of the first patients having achieved remission, the relapses are rare but early (up to 2 years), and the risk of transformation or dissemination is also low, as shown in the study by Zullo et al. [28], pulling together the results of 32 published series (1271 cases of gastric lymphomas treated with antibiotics) [28].

6.1.1.2. Treatment in case of non-regression of the lymphoma after eradication of H. pylori. Radiotherapy or chemotherapy can be proposed in case of non-regression after the eradication of *H. pylori* (large tumour mass, non-regression of endoscopic lesions, lymphomatous infiltrate persisting after at least 24 months of follow-up), or in *H. pylori*-negative lymphomas, or those with t(11;18) translocation, less susceptible to respond to eradication treatment. Surgery is only proposed in case of perforation or haemorrhage uncontrolled by endoscopic treatment, which is extremely rare.

6.1.1.3. Radiotherapy. Low-grade small B-cell NHL are sensitive to low doses of radiotherapy. For localised gastric lymphomas, exclusive radiotherapy used in case of failure of antibiotics treatment gives very good results without long-term side-effects [31]. The first published results, based mainly on small, retrospective series of patients (n = 6–20 gastric MALT lymphomas), showed a complete remission rate of 96–100% fora median follow-up of 1.3–4.1 years [32–36]. The excellent results and good tolerance of the low-dose (30 Gy) radiotherapy, have been recently confirmed by a larger prospective French GELD/FFCD study including 53 patients with a long-term follow-up (median of 4.9 years), showing a response rate of 98% and an overall survival linked to the lymphoma of 94% [37]. The recommended dose in conformational radiotherapy is 30 Gy in classic fractionation (1.8–2 Gy/session and 5 sessions per week) delivered on the gastric volume and the epigastric lymph nodes [37,38].

6.1.1.4. Chemotherapy and immunotherapy. Chemotherapy has been mainly assessed for extra-nodal disseminated MALT lymphomas, more rarely for localised gastric lymphomas [17]. In a phase III trial of 401 patients with localised or disseminated MALT lymphoma of gastric or other origin, the regimen combining rituximab and chlorambucil proved to be better than chlorambucil or rituximab used in monotherapy, with a response rate of 80%, 62% and 55%, respectively, and the corresponding 5-year progression-free survival rate of 72%, 59% and 58% [39]. These differences in overall survival were found in all patients but also in subgroups, in particular in the subgroup of gastric MALT lymphomas.

Maintenance therapy with rituximab with an infusion of 375 mg/m^2 every 2 months for 2 years has only shown first-line benefit in nodal follicular lymphomas [40]. For other indolent lymphomas, both non-follicular and MALT lymphomas, maintenance therapy is not recommended and is being currently assessed in all loc alisations of MALT lymphomas in phase II IELSG Trial. Also, although proposed by some authors in localised forms, chemotherapy should be rather reserved for disseminated MALT lymphomas. Polychemotherapy regimens containing anthracyclines should be proposed only for the cases of histological transformation into aggressive lymphoma and are not justified in first-line treatment (expert opinion).

Some long-term complications of chemotherapy in indolent MALT lymphomas have been reported, particularly a significant increase of secondary cancers [41]. The option of surveillance ("watch and wait" strategy) after antibiotics treatment can also be discussed (in case of so-called microscopic lymphomatous residual disease, in the absence of endoscopic lesions, in elderly patients, in patients with comorbidities) [30].

6.1.2. Diffuse large B-cell lymphomas (DLBC)

6.1.2.1. Recommendations. The reference treatment is a R-CHOP chemotherapy regimen combining rituximab with CHOP (doxorubicin, cyclophosphamide, vincristine, prednisone) for 6 or 8 cycles every 3 weeks [42].

Systematic eradication of *H. pylori* is recommended with the aim to treat the potentially associated proliferation of small MALT-type B-cells [43].

6.1.2.2. Options. In young subjects with a large disseminated tumour mass (stage IV, elevated LDH), which is rare in PGIL, the indication of intensifying chemotherapy with autologous stem cell transplantation, can be discussed with haematologists. There is no indication of radiotherapy in DLBC digestive lymphomas.

6.2. Intestinal B-cell lymphomas

Different forms of these lymphomas, defined according to their cellular origin, have different prognosis and, accordingly, they require different therapeutic strategies [10,44].

6.2.1. Intestinal DLBCL

The most frequently they are treated by chemotherapy combined with rituximab, just like DLBCL of other localisations. The treatment strategy and its duration depend on the initial prognostic analysis (cf supra stomach NHL)

The only indication of surgery are complications, generally inaugural (obstruction, perforation, etc.). In this case, surgery is usually followed by adjuvant chemotherapy (4 cycles of R-CHOP) (expert agreement) [4,42].

6.2.2. Mantle cell lymphomas

This is the most frequent histologic type of intestinal lymphomatous polyposis. These lymphomas are often disseminated with multifocal involvement of several segments of the digestive tract. Localisations in the lymph nodes, bone marrow and blood are frequent. They are characterised by a relative chemoresistance and unfavourable evolution after chemotherapy at conventional doses [9,45,46]. Currently, the young patients (under 65 years of age) undergo R-DHAX (P or C) type induction therapy, followed by consolidation with intensification and autologous hematopoietic stem cell transplantation, and maintenance therapy with rituximab for 2 years. The treatment is realised in haematology departments.

In patients over 65 years of age and under 80, the treatment with R-CHOP with maintenance therapy with rituximab for at least 2 years is the current recommendation [9,47].

6.2.3. Extra-nodal marginal zone lymphoma of MALT

Unlike gastric marginal zone lymphomas of MALT, those lymphomas localised in the intestine are rare and there is no consensus on their management. In localised forms, abstaining from therapy can be justified. In the other cases, the treatment of reference is a combination of rituximab and an alkylating agent (chlorambucil). R-CHOP combination must be reserved for cases with suspicion of transformation. Radiotherapy is not possible due to intestinal mobility and related risk of toxicity.

6.2.4. Follicular lymphomas

Probably due to their better identification, primary follicular lymphomas (small B-cells) of the digestive tract are more frequently diagnosed and it seems that they are not as rare as it was previously thought. They are in general found in the small intestine and are often discovered fortuitously. They may be localised (in the duodenum for example) or multifocal in the digestive tract with sometimes endoscopic aspect of lymphomatous polyposis [48–50].

Initial abstaining from therapy is justified in the asymptomatic forms with low tumour mass (GELF criteria), like in nodal forms of follicular lymphomas, whatever the patient's age [51].

The treatment is indicated in the symptomatic tumours and/or those with high tumour mass (GELF criteria). The reference treatment is the combination of CVP or CHOP chemotherapy combined with rituximab, followed by the maintenance therapy with rituximab at 375 mg/m^2 every 2 months for 2 years.

6.2.5. Burkitt lymphomas

These lymphomas are usually observed in children and young adults; digestive presentations, particularly ileo-caecal, are not rare. Initial chemotherapy in an urgency and should be performed in a specialised haematology department [52]. Intensive chemotherapy regimens, including a prophylactic intrathecal treatment and adapted to the initial prognostic factors, allow achieving a high cure rate. They comprise an anthracycline, cyclophosphamide, high doses of methotrexate and cytarabine. Surgery is not indicated, except for an emergency surgery in case of complications.

6.2.6. Immunoproliferative small intestinal disease (IPSID) — alpha chain disease

IPSID are mainly represented by the alpha chain disease (ACD), described especially in young patients living around the Mediterranean basin, decreasing in prevalence and almost disappeared in Western countries. ACD corresponds to an extranodal marginal zone MALT lymphoma affecting the exocrine IgA mucosal system [53]. A study has highlighted the pathogenic role of *Campylobacter jejuni* in tumour proliferation [54]. The lymphoma is primarily localised in the small intestine and in the mesenteric lymph nodes but can affect the stomach, colon, rectum, the more distal and peripheral abdominal lymph nodes, the Waldeyer's ring, the bone marrow and other organs.

The disease progresses from a plasmocyte stage of a low degree of malignancy (stage A) to an immunoblastic stage of a high degree of malignancy (stage C). In the intermediate stage B, the cellular infiltrate is made up of dystrophic plasmocytes and a small number of immunoblasts. Different grades of malignancy can be observed at the same time at different sites, and thus an exhaustive work-up is necessary.

The therapeutic strategy depends on the patient's age and general status, which can be altered at all stages, both because of associated malabsorption/exudative enteropathy and of the tumour itself. An appropriate diet, enteral or parenteral nutrition is necessary, and specific deficiencies (iron, folates, calcium, magnesium, oligo-elements, vitamins, etc.) must be corrected.

The choice of the treatment depends on the grade of malignancy (definitions specific to the ACD):

- the lesions at stage A, limited to the gastro-intestinal tract and to the satellite lymph nodes, are treated by oral macrolide or tetracycline antibiotics, combined with anti-parasitic treatment. Out of 28 patients treated in this way, 39% achieved a complete remission [53]. Because of the unpredictable character of the progression of stage A towards the stages of higher degree of malignancy, chemotherapy must be started early enough (quite rapidly) in patients who don't respond to antibiotics;
- the patients with stages B and C (transformation into large B-cells lymphoma), besides the antibiotic and anti-parasitic treatment which can improve the malabsorption syndrome, should receive chemotherapy including an anthracycline (R-CHOP) if only nutritional and digestive status allows it. Some patients have benefited from intensification with autologous stem cell transplantation (expert opinion).

6.3. Intestinal T-cell lymphomas

Intestinal T-cell lymphomas are rare, representing less than 1% of all NHL. The unfavourable prognostic character of the T phenotype is well established. There are currently no specific recommendations for the clinical management of these lymphomas.

Besides the intestinal localisations of virus-induced T-cell lymphomas (linked to HTLV-1 or to EBV like nasal T or NK/T-cell lymphomas), those linked to immune deficiencies, orCD4+ T-cell lymphomas of the chorion [55], we can distinguish T-cell lymphomas associated with enteropathies, in particular with celiac disease [56,57].

The lymphomatous complications of celiac disease are rare (<3/100,000 inhabitants per year), but very severe. Two types of refractory celiac disease have been identified, known as non-clonal type I refractory sprue (RS I) and clonal type II refractory sprue (RS II). RS II is considered as a lymphoma of low grade of malignancy which is intraepithelial, associated with celiac disease and characterised by an expansion of small intraepithelial lymphocytes (IEL) of abnormal phenotype (no expression on the surface of the CD3 T-cell receptor complex, but intracellular CD3+ by IHC and CD8−, CD103+) [57]. It progresses into T-cell lymphomas with a high grade of malignancy in 30–50% of cases at 5 years and its prognosis is poor with less than 45% of patients still alive 5 years after diagnosis [58]. Diagnosis is difficult and requires specific immunohistochemical, phenotypic and molecular studies (PCR Multiplex). Coming from the small intestine, the abnormal IEL of the refractory sprue can spread within the entire digestive tract (distal small intestine, stomach, colon), circulate in the blood and invade the bone marrow and various epithelia such as the skin, the lungs, and the sinuses because of their epitheliotropic nature. More recently, granular leukaemias (LGL, Large granular lymphocytic Leukaemia) have been identified, which, from the periphery, invade the intestine of celiac patients, leading to the resistance to a gluten-free diet. LGL should be distinguished from RS II which is the first differential diagnosis to consider, since it is also characterised by the persistent malabsorption syndrome, villous atrophy and an intestinal T-cell clone in celiac patients. Flow cytometry enables the diagnosis by showing the usual expression of CD8 and CD57 markers in these patients [59].

The poor prognosis of the RS type II is linked to the absence of efficient treatments as those currently used (corticosteroids and immunosuppressive drugs) bring only a partial and temporary response [58]. Two new therapeutic strategies for RS II are being currently evaluated by National French Expert Centre for Lymphomas Associated with Celiac Disease ("CELAC"): (1) a classical treatment with chemotherapy–autograft, and (2) a targeted therapy with anti-IL-15 agents. The objective is to cure patients with RS II and to prevent the appearance of T-cell lymphomas with a high grade of malignancy called "Enteropathy Associated T-cell Lymphoma" (EATL). These T-cell lymphomas are rare (estimated incidence of 0.22–1.9/100,000 inhabitants) [60] but of a poor prognosis with a survival rate not exceeding 20% at 5 years. The EATL can be diagnosed during emergency surgery and can reveal celiac disease. Conversely, when celiac disease is known, the lymphoma must be screened in case of a resistance to a gluten-free diet, and its diagnosis can be difficult. It is done by enteroscopy, CT-Scan of the chest and abdomen, PET-Scan or even laparotomy or exploratory laparoscopy.

The management and treatment of EATL should be always discussed in the multidisciplinary meeting. Nutritional status, possibility of using chemotherapy and surgical reduction of the tumour are independent prognosis factors in EATL survival in uni-and multivariate analysis [61]. Given the fact that more than 80% of EATL are CD30+, a phase 2 clinical trial using anti-CD30 antibody is currently open in France (Phase 2 Study of Brentuximab Vedotin and CHP followed by autologous stem cell transplantation as frontline treatment of enteropathy-associated T-cell lymphoma).

7. Surveillance

7.1. After immuno-chemotherapy or radiotherapy

Classically, the surveillance of lymphomas after chemotherapy and/or radiotherapy includes a post-treatment work-up and then an annual check-up for 10 years comprising: clinical examination, biological tests (LDH, beta 2 microglobulin, hepatic biology) and in some cases, according to the type of lymphoma, a CT-scan of the abdomen and chest, as well as an endoscopic examination of the main site initially affected.

7.2. Non-standardised attitude adjusted to the histological type (experts' agreement)

1. For high grade of malignancy lymphomas, clinical monitoring every 6 months for the first 2 years, then once a year, with clinical and endoscopic examinations and measurement of LDH levels, can be proposed. The proposed length of follow-up varies from 5 to 10 years (expert opinion), and no imaging examination (CT scan or FDG-PET) is recommended. The optimal frequency of endoscopic tests is not determined.
2. For the low grade of malignancy lymphomas, because of a permanent risk of relapse (follicular NHL), a regular long-term monitoring and further examination according to clinical signs, are indicated.

For marginal zone MALT lymphomas, after *H. pylori* eradication, annual clinical and endoscopic monitoring for at least 10 years has been proposed. However, monitoring from 5 years onwards can be spaced out (but there is no standardised scheme) [7]. Surveillance of the remaining stomach is extremely important, especially in the presence of intestinal metaplasia or dysplasia on gastric biopsies, because of an increased risk of adenocarcinoma in these patients. Indeed, the cases of gastric adenocarcinoma have been observed during the follow-up of cured lymphomas [28,30,62,63]. Furthermore, the epidemiological study of Capelle et al. [64] from the Netherlands showed that the risk of gastric adenocarcinoma in patients with a history of gastric lymphoma was multiplied by 6 as compared to the general population [64].

8. Treatment of recurrence

In gastric MALT lymphomas, a true relapse is an exception and usually corresponds to incompletely regressed lymphoma, sometimes related to the persistence of *H. pylori* infection. In these cases, and if the absence of bacteria is confirmed, an alternative treatment should be proposed.

In other histological subtypes, especially of high grade of malignancy, and in other localisations, relapses have much poorer prognosis. These patients should be managed in haematology department. Salvage chemotherapy regimens consist in protocols combining platinum, etoposide, high doses of cytarabine or ifosfamide and etoposide. In young patients, intensification with autologous hematopoietic stem cell transplantation may be considered.

Conflict of interest

None declared.

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