Introduction

Primary lymphomas of the digestive tract are non-Hodgkin lymphomas (NHL), by definition arising from MALT (mucosa-associated lymphoid tissue), comprising different clinicopathologic entities that should be known because their specific clinical feature, prognosis and treatment. Rare are the prospective studies that take into account recent pathological classification and that propose homogenous treatment [1-5]. Even though gastrointestinal locations are the most frequent of the extranodal NHL, these tumors remain rare, which, together with the diversity of anatomical and clinical forms, explains why it is difficult to conduct randomized therapeutic trials. Management of these tumors, notably the therapeutic strategies, are specific to their digestive system location. When chemotherapy is indicated it is generally conducted by the results obtained with nodal NHL, which are much more frequent.

Diagnostic criteria – anatomical and pathological classifications

Diagnostic

The diagnosis of lymphoma is made on:
- endoscopic biopsies [1, 3, 6, 7], more rarely for emergency surgery for digestive tract hemorrhage or obstruction (small intestine location).
- placed in 10 % neutral buffered formalin or AFA (alcohol-formalin-acetic acid) for morphology and immunohistochemical study and now cytogenetic or molecular biology
- frozen tissue, not mandatory but recommended; allows molecular biology studies, rarely useful for diagnosis and therapeutic decision, but usually required within protocol studies.
- For gastric tumor, Helicobacter pylori testing is systematic: on histology; culture on Portagerm is sometimes useful for the antibiogram when there is resistance to treatment; systematic serology, especially in absence of Helicobacter pylori on histology [7-9].

Positive Helicobacter pylori status is defined as a positive histology or serology [10].

ANATOMICAL AND PATHOLOGICAL CLASSIFICATIONS

Annex I

The different types gastrointestinal lymphomas have been recognized and listed by P. ISAACSON [11], but the latest WHO classification (2001) is the current reference; diagnosis should follow this classification where the NHL are furthermore charactarised through morphological, molecular biological, etiopathogenetical and biological aspects [12].

Leading to prognostic and therapeutic implications, the histological subtype of the lymphoma should be precisely established. The opinion of an experienced pathologist is often useful for diagnosis (second reading of slides and occasionally complementary techniques).

Most often B lymphoma is diagnosed (90% of cases), more rarely T lymphoma. It appears that most primary lymphomas of the digestive system arise from MALT (mucosa-associated lymphoid tissue). The indolent course characterizes small B cell low-grade lymphomas distinct from spontaneously aggressive large B-cell high-grade types [13]. In Western countries, gastric lymphomas are the most frequent.

Pretherapeutic explorations: clinical stage

This workup is generally the same whatever the histological sub-type and site of lymphoma [3, 7, 14].

Assessment of extension (expert agreement)

CLINICAL EXAMINATION

- performance status (WHO)
- B symptoms
- Physical examination: peripheral lymph node, liver, spleen, ENT.

LABORATORY PARAMETERS

Reference

Hemogram; liver tests; electrophoresis and immunofixation of blood proteins; serum LDH and β2-microglobuline levels; uricemia; HIV serology

Alternatives
debatable advantage or according to lymphoma type:
Helicobacter pylori serology (gastric lymphomas, especially if negative histology); hepatitis B and C serology; uricemia; anti-endomysium and anti-transglutaminase antibodies (T lymphomas). Search for monotypic B lymphoid subpopulation in blood.

ENDOSCOPIC AND RADIOLOGIC DIGESTIVE TRACT WORK-UP

Reference

Digestive tract endoscopy: esogastroduodenoscopy and ileocolonoscopy with systematic biopsies even when there is no macroscopic lesion.
Small bowel enema
Endosonography (EUS) for stomach lymphoma: initial prognostic value and follow-up [8,15-17].

Alternatives

debatable advantage or according to lymphoma type:
Enteroscopy if intestinal biopsies are necessary for diagnosis;
Endosonography for esophagus or rectum locations.

OTHER EXPLORATIONS

Reference

computed tomography (CT) of the thorax and abdomen
CT and/or endoscopy of the cavum and biopsies if there is doubt;
Bone marrow biopsy

Alternatives

debatable advantage or according to lymphoma type:
Heaptic needle biopsy exceptionally needed (particularly since the diagnostic sensitivity is poor.

Cerebro spinal fluid study (with cytocentrifugation) for disseminated high-grade lymphomas or those with a important tumor mass or high grade and Burkitt lymphomas.
ECG and isotopic myocardial function study: systolic ejec-
tion fraction or cardiac ultrasound if chemotherapy with anthra-
cyclines is planned.

Clinical stage

Annex II

The Ann Arbor staging system modified by Musshoff reports the results of the extension assessment [18]. Primary digestive tract lymphomas are generally localized (70%); stage IE (digestive wall involvement) or stage IIE1 (lymph node involvement in the tumor area), or IIE2 (distant lymph node involvement, poor-
er diagnosis). Other, more specific staging systems for digestive tract are being evaluated by European EGILS (European Gastrointestinal Lymphoma Study) group: staging system inspired by the TNM staging system for lymphomas was recently published (Paris staging system) [19]. Specially useful for staging of local extent of the disease it adequately records depth of the tumor infiltration and extent of nodal involvement, notably for gastric staging assessed by endosonography (EUS).

Other than the clinical stage, prognostic parameters have been identified by the International Prognostic Index for NHL. For lymphomas labeled as aggressive with high grade of malignancy, this index conditions the prognosis and therapeutic decision. It takes into account age, the WHO index, the LDH blood level, and the number of extranodal sites involved. This index can be adapted for gastrointestinal high grade lymphomas, although in this location the vast majority of large-cell lymphomas are often good prognosis as they are often localized, with a good WHO prognosis index and a normal LDH blood level [3].

Treatments

Gastric B lymphomas

LYMPHOMAS OF THE MARGINAL ZONE OF MALT (SO-CALLED LOW-GRADE)

Methods and strategy:

Reference

Eradiation of Helicobacter pylori: should be performed pri-
marily, specially for Helicobacter pylori-positive status lympho-
mas (positive histology and/or serology)
For the moment, it is advised in all gastric lymphomas, even if the Helicobacter pylori status was negative. The different published series report variable remission rates depending on the work-up and initial clinical stage. Therefore, chances of complete remission are 80% for the IE stage tumors (initially evaluated with EUS) and positive Helicobacter pylori status: [8, 20-26]. The current follow-up of the first patients reported in remis-
sion is 8 years [27-30], the relapses observed are extremely rare but generally in the early course (2 years).

What to do and results of Helicobacter pylori eradication [8]

• Initial EUS is important for prognosis a prognostic with a predictive value of lymphoma regression after eradication of the bacterium [8, 16, 17, 31, 32] and is very important for follow-up.
• Triple therapy given during 7 or 14 days to eradicate the bacterium (per 24 h in two sessions: IPP x 2, amoxicillin 1 g x 2, clarithromycin 500 mg x 2). If therapy fails, see antibiogram or replace clarithromycin with metronidazole
• Check endoscopy at 1 month after treatment verifying that Helicobacter pylori has been well eradicated and that there is no local progression of the lymphoma.
• Endoscopic and EUS (if doubt of progression ) follow-up every 4 months for 1 year, then every 6 months the second year, then every year.

Complete remission is confirmed by endoscopy and and EUS but is defined on histology: disappearance of all morpho-
logically lymphomatous cells at 24 months (median of remission onset, 6 months; range, 3–24 months). Remission can only be confirmed after at least two successive negative endoscopic biopsies (expert opinion).

If at 2 years, or even longer, a so-called minimal residual lymphomatous disease defined histologically by a few patholo-
gically lymphoid islets, persists; its outcome is not clearly known [30]. Currently, this is considered as antibiotic treatment failure and requires a therapeutic alternative specially for younger patients.

Alternatives

The therapeutic alternatives (surgery, radiotherapy, or chemotherapy) can be proposed for failure of remission after...
eradication of Helicobacter pylori (bulky tumor mass, nonregression of lesions identified with endoscopy, residual lymphomatous infiltrate after 24 months of treatment) or the Helicobacter-negative status lymphomas, which a priori do not regress after antibiotic therapy.

Surgery

The results of radical surgery reported in the literature show 88%-100% of 5-year disease free survival (with 40-96 months of follow-up) [33]. These series concerned patients diagnosed before the role of Helicobacter pylori was demonstrated. In terms of efficacy on the disease, surgery was the reference treatment for gastric lymphomas (level B). However, the requirement for total gastrectomy (multifocal lymphomas and endoscopically echoendoscopic explorations that are not sensitive enough to determine its extension [15]) moreover for often residual lymphomas after antibiotics and indolent course lymphomas, made considering more reasonable alternative therapies such as radiotherapy or chemotherapy.

Radiotherapy

Annex III

Small B-cell, low-grade NHL are sensitive to low doses of radiotherapy [34, 35]. For gastric lymphomas, the results of exclusive radiotherapy in case of antibiotic treatment failure are currently being evaluated. The first results published come from small series with a mean follow-up of 5 years; leading to the proposal of radiotherapy as a therapeutic alternative to surgery (level of evidence D and open trials in progress) [36-38]. The doses usually recommended in conformational radiotherapy are 30 Gy in conventional fractioning (1.8-2 Gy/session and 5 sessions a week) on the gastric volume and the perigastric lymph node areas.

Chemotherapy

Annex IV

These long-term results are disappointing for small B-cell low-grade lymphomas; they have rarely been evaluated in localized gastric NHL. The rare studies with oral monochemotherapy (fewer than 20 patients) report initial response rates ranging from 34% to 75%, with relapse-free survival and 5-year overall survival 50% and 75%, respectively, but with follow-up that is still too short given the natural history of the disease (10-year survival) [39, 40]. These results do not lead to systematically recommend chemotherapy. However, it is indicated for the rare disseminated stage IV lymphomas.

However, after publication of preliminary results in a few cases, therapeutic trials, specific to marginal zone of MALT gas- tric lymphomas disseminated or localized, are currently in progress to evaluate the advantages and tolerance of rituximab (anti-CD20 immunotherapy) combined or not with per oral alkylating agents [41-43] (level D).

Clinical trials and studies

- Localized MALT-type gastric lymphomas after Helicobacter pylori eradication: prognostic factors and clinical monitoring with satellite molecular biology studies: GELD protocol, (coordinator: Dr. A. Ruskoné-Fourmestraux, Hôpital St Antoine, 75012 Paris. Tel: 01 49 28 31 72. E-mail: agnes.fourmestraux@sat.aphp.fr) pathological coordinator; Pr JF Flejou, hôpital St Antoine, 75012 Paris. Tel: 01 49 28 21 70.
- Monitoring and long-term follow-up in patients operated on before 1991: GELD study, FFCD, (coordinator: Dr. A. Ruskoné-Fourmestraux) • Localized MALT-type gastric lymphomas after failure of antibiotic therapy or negative Hp status: evaluation of low-dose conformation radiotherapy: open trial began in 2001 in collaboration with European teams and GELD, FFCD (coordinator: Dr. A. Ruskoné-Fourmestraux, Hôpital St Antoine, 75012 PARIS. Tel: 01 49 28 31 72. E-mail: agnes.fourmestraux@sat.aphp.fr)
- Extranaud disseminated or localized forms, de novo or after antibiotic or radiotherapy failure: evaluation of alkylating agents combined or not with rituximab: international trial and GELA, coordinator in France Dr. C. Thieblemont, Hematology Unit Hôpital Lyon-Sud. Tel: 04 72 66 93 33. E-mail: catherine.thieblemont@chu-lyon.fr)

**DIFFUSE LARGE B-CELL LYMPHOMAS (HIGH-GRADE)**

Reference - method

Chemotherapy is the reference treatment for this sub-type of lymphoma. The reference for NHL is CHOP (doxorubicin, cyclophosphamide, vincristine, prednisone). This is now almost systematically associated with rituximab. It has been demonstrated for nodal NHL that the combination of rituximab and conventional chemotherapy (R-CHOP protocol) achieved better response and survival rates than CHOP alone [44]. ANNEX IV.

Eradication of Helicobacter pylori is systematically associated in view of treating the possible proliferation of MALT-type small B-cells.

Strategies

- For localized stage IE forms, surgical resection (R0) has proven effective and was usually followed by chemotherapy (4 courses of CHOP, expert opinion) (90%-100% cure). Chemotherapy alone (CHOP, 6 courses) can also be effective, including in the elderly subject with good tolerance (CHOP or mini-CHOP), as two recent studies have shown [4, 5]. The combination with rituximab [43] is also increasingly used considering the results in NHL of all stages (level B) [44]. However, no controlled study has yet been conducted to confirm that it is superior to CHOP alone in localized gastric lymphomas.
- For disseminated disease or those with important tumor mass with high LDH blood level, R-CHOP chemotherapy is advised.
- For so-called bulky localized tumors with locoregional lymph node extension, the efficacy of chemotherapy reduces the interest of first-line surgical resection, which was controversial: although useless (because it contributes no survival advantage) for some [5, 45], it improves the prognosis for others [1, 3].

Alternatives

In the young patient and more particularly in the patient presenting a bulky and disseminated tumor mass (stage IV), a rare occurrence, intensification of the chemotherapy combined with autologous hematopoietic stem cell transplantation should be discussed with the hematologists of a specialized center. In these cases, preventive intrathecal chemotherapy is also administered.

The place of radiotherapy remains very limited, in exceptional cases of partial response (residual tumor mass) after first-line chemotherapy.
Intestinal B lymphomas

Methods and strategies:

LYMPHOMAS OF THE MARGINAL ZONE OF MALT (LOW-GRADE LYMPHOMAS)

Contrary to MALT gastric lymphomas, therapeutic management of marginal zone lymphomas of the MALT located in other sites of the digestive tract (much rarer) has not met with consensus. Abstention from therapy can be warranted in apparently localized forms that have been operated on (for diagnostic purposes). In other cases, no argument has been put forward attesting to the superiority of polychemotherapy (e.g., CHOP) over oral monochemotherapy using an alkylating agent (chlorambucil or cyclophosphamide) combined or not with rituximab. No trial on radiotherapy for intestinal lymphomas is planned.

LARGE-B CELL DIFFUSE LYMPHOMAS

The treatment of large-cell diffuse lymphomas is based on chemotherapy as it is used in large B-cell NHL, the therapeutic protocol used and the duration of treatment depending on the analysis of the initial prognostic parameters. In these intestinal lymphomas, surgery is sometimes necessary for diagnostic purposes or to treat an early complication. In cases of first-line surgery, it is advised to plan for adjuvant chemotherapy (4 courses of CHOP) (expert opinion). Adding rituximab to CHOP is increasingly systematic in cases of first-line chemotherapy.

MANTLE-CELL LYMPHOMAS (LYMPHOMATOUS POLYPOSIS)

This sub-type of lymphoma mostly but not exclusively presents as a lymphomatous polyposis. These lymphomas are the most often disseminated (stage IV) with multifocal digestive tract involvement extended to several segments of the digestive tract. Peripheral nodal, bone marrow and blood involvement, are frequent. They are characterized by relative chemoresistance and poor prognosis after chemotherapy at conventional doses [46].

Currently, the youngest patients (<65 years) can undergo intensive therapy best managed in hematology units. The use of high doses of cytarabine (Aracytine®) in initial chemotherapy protocols and intensification with autologous hematopoietic stem-cell transplantation at the first remission significantly prolongs the duration or remission. Rituximab is now associated with chemotherapy in the context of intensive treatments [47].

In elderly subjects, there is no consensus on treatment, and CHOP treatments combined with rituximab remain the most frequently used.

FOLLICULAR LYMPHOMAS

Since they are better identified, primary follicular lymphomas of the digestive tract are not as rare as has been thought to date. They are generally located in the intestine, sometimes in apparently localized forms (e.g., duodenal) or disseminated in the digestive tract, with occasionally a lymphomatous polyposis presentation at endoscopy.

Following the example of nodal forms of follicular NHL, abstention from initial therapy is warranted in asymptomatic forms with low tumor mass, whatever the patient’s age. When treatment becomes necessary (symptomatic forms and/or bulky tumor mass criteria), the reference treatment is based on combination chemotherapy associating CVP or CHOP with rituximab [48]. The advantage of interferon, which was used in France for years in association with chemotherapy, is more difficult to justify since rituximab came into use.

In young patients with extensive disease after the first remission an early intensified regimen with autologous hematopoietic stem cell transplantation (usually carried out as second- or third-line therapy) has not yet been shown to be superior to a conventional therapy approach.

BURKITT LYMPHOMAS

Burkitt lymphomas are more often observed in children and young subjects, in whom digestive tract presentations, notably ileoceleal locations, are not rare. Intensive chemotherapy including prophylactic intrathecal treatment (practiced in specialized hematology units) adapted to initial prognostic factors can obtain a high cure rate. The include anthracycline, cyclophosphamide, methotrexate at high doses, and cytarabine. If the diagnosis is established with no complication that requires immediate surgery, there is no place for surgery in the treatment regimen.

T cell GI lymphomas

T cell digestive system lymphomas are very rare and have a poor prognosis. It has now been established that the T phenotype has poor prognostic significance, calling for alternative therapeutic approaches. There are currently no specific recommendations for digestive tract T cell lymphomas [49].

IPSID – alpha chains disease

Immunoproliferative small-intestine disease (IPSID) is more and more rare and is located in the small intestine and in the mesenteric lymph nodes, but also in the stomach, rectal colon, the more distal and peripheral abdominal lymph nodes, the Waldeyer ring, bone marrow, and other peripheral organs and tissues [50].

In addition, the disease progresses in three increasing malignancy grades. Most particularly, different histological grades can be observed at the same time from one site to another, on the same or different organs. Assessment of extension is therefore necessary. The future will tell whether current tests can avoid laparotomy, an element of the reference work-up.

The indications for therapy take into account the patient’s age and general condition. The latter can be altered at all histological grades of the disease from both the exudative malabsorption/enteropathy and the tumor itself. Depending on the case, appropriate diet, or enteral or parenteral nutrition are necessary. Specific deficiencies (iron, folates, calcium, magnesium, trace minerals, vitamins, etc.) should be corrected. Beyond their specific effect on tumor proliferation, as a general rule antibiotics have a spectacular effect on diarrhea and malabsorption (tetracycline, metronidazole). These nonspecific measures are mandatory to the success of the antitumor treatment.

Treatment depends on the grade of the disease.
LOW-GRADE IPSID

Grade A= B cell MALT lymphoma, particular in the plasmocyte amount and differentiation at a cytological level, localized to the small intestine ± mesenteric lymph nodes:

- Initial exclusive antibiotic therapy with tetracyclines (2 g/day): 40% prolonged complete remission.
- Duration of initial treatment, 6 months. If partial response at 6 months, renew for 6 months.
- If there is no response at 6 months or complete nonremission at 1 year, change to chemotherapy corresponding to the next grade.

INTERMEDIATE-GRADE IPSID

Grade B or high grade C localized to the small intestine and/or mesenteric lymph nodes, and antibiotic therapy failure in grade A.

- Polychemotherapy including an anthracycline (CHOP): 63% complete remission in grades B and C, few complete remissions at grade A.

PRECEDING OR IMMEDIATE TREATMENT FAILURE IN CASES OF DISSEMINATED GRADE C DISEASE:

- Intensive chemotherapy and autologous graft, but prognosis is poor and recurrence rapid; in our experience, the disease has never been eradicated, even transitorily (expert opinion).

Follow-up after treatment

Except for the monitoring described above for gastric MALT lymphomas after eradication of Helicobacter pylori.

After chemotherapy, surgery, radiotherapy

Conventionally, monitoring lymphomas after chemotherapy and/or surgery and/or radiotherapy stipulates a work-up after the end of treatment, then annually for 10 years, including clinical examination, biochemical tests (LDH level, beta 2 microglobulinemia, liver tests), thoraco-abdominal CT and endoscopic examination of the initially involved sites. Bone marrow biopsy is only necessary if the bone marrow was also initially involved.

Follow-up adapted to the histological type (expert agreement).

1. High-grade malignancy: clinical follow-up every 4 months for the first 3 years, then progressively spaced out, because maximum risk of relapse during the first 3 years. Biochemical tests with DH level. The optimal frequency of endoscopic and CT follow-up is undetermined, but several studies have shown little advantage to CT-scan examination at predetermined times: recurrence often occurs between follow-up examinations (expert agreement).

2. Low-grade malignancy: permanent risk of recurrence requiring long-term (10 yrs) regular monitoring and complementary tests based on clinical signs. For MALT-type lymphomas, monitoring the stomach because cases of gastric adenocarcinomas have been reported during follow-up of cured lymphomas.

Treatment of recurrences

Relapses are rare for marginal-zone MALT lymphomas of the stomach, but possible, and they carry a poor prognosis in other locations and histological types. Salvage chemotherapy is based on protocols combining high doses of platinum, etoposide, and aracytine or ifosfamide and etoposide. In young responders, intensification can be planned with autologous hematopoietic stem cells transplantation.

ACKNOWLEDGMENTS TO READER: Laurent Bedenne (HGE, CHU Dijon).
### Annex. I

Different types of GI lymphomas listed by P. G. ISAACSON and WHO classification (2001)

<table>
<thead>
<tr>
<th>B Phenotype</th>
<th>Marginal zone of MALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>low-grade</strong> B-cell lymphoma of the MALT* type.</td>
<td></td>
</tr>
<tr>
<td>- of the Western type (localized)</td>
<td></td>
</tr>
<tr>
<td>- of the Mediterranean type (extensive): IPSID*</td>
<td></td>
</tr>
<tr>
<td>(essentially alpha-chain diseases)</td>
<td></td>
</tr>
<tr>
<td>• <strong>high-grade</strong> B-cell lymphoma of the MALT* type.</td>
<td></td>
</tr>
<tr>
<td>With or without low degree of malignancy including</td>
<td></td>
</tr>
<tr>
<td>- centroblastic</td>
<td></td>
</tr>
<tr>
<td>- immunoblastic</td>
<td></td>
</tr>
<tr>
<td>- large anaplastic cells</td>
<td></td>
</tr>
<tr>
<td>• Centrocytic lymphoma = lymphomatosus polyposis</td>
<td>Mantle zone lymphoma</td>
</tr>
<tr>
<td>• Burkitt or Burkitt-type lymphoma</td>
<td>Burkitt</td>
</tr>
<tr>
<td>• Other types (equivalent to lymph node lymphomas)</td>
<td>Follicular</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T Phenotype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• T cell (EATL*) associated with enteropathy</td>
<td>Intestinal T cell</td>
</tr>
<tr>
<td>• T lymphomas not associated with enteropathy</td>
<td></td>
</tr>
</tbody>
</table>

* MALT = mucosa-associated lymphoid tissue  
* IPSID = immunoproliferative small-intestinal disease  
* EATL = enteropathy-associated T lymphoma

### Annex. II

Clinical stages for non-Hodgkin lymphomas. Ann Arbor staging system modified by Musshoff for the digestive tract

<table>
<thead>
<tr>
<th>Stage $I_e$</th>
<th>Involvement of one site of the digestive tract with no lymph node involvement.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage $II_e$</td>
<td>Involvement of one site of the digestive tract and regional lymph nodes with no extra-abdominal involvement. Musshoff modification: stage $III_e$= involvement of only contiguous lymph nodes; stage $II_2_e$= involvement of regional noncontiguous lymph nodes.</td>
</tr>
<tr>
<td>Stage $III_e$</td>
<td>Localized involvement of digestive tract associated with lymph node involvement of both sides of the diaphragm*.</td>
</tr>
<tr>
<td>Stage $IV$</td>
<td>Involvement of one or several extranodal and/or extra-abdominal organs with or without associated lymph node involvement.</td>
</tr>
</tbody>
</table>

*Stage not generally encountered in digestive system lymphomas.

A new staging system that is better adapted to the digestive tract was drawn up by the European EGILS (European Gastrointestinal Lymphoma Study). Group ref A. Ruskoné-Fourmestraux, Gut, 2003.

**PARIS STAGING SYSTEM for GI lymphomas**

<table>
<thead>
<tr>
<th>TX extension not specified</th>
<th>TO no lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1m mucosa involvement</td>
<td>T1sm submucosa involvement</td>
</tr>
<tr>
<td>T2 involvement of the muscularis propria or subserosa</td>
<td>T3 serosa involvement</td>
</tr>
<tr>
<td>T4 invades adjacent structure or organs</td>
<td></td>
</tr>
<tr>
<td>NX lymph node involvement not assessed</td>
<td>NO no lymph node involvement</td>
</tr>
<tr>
<td>N1 regional lymph node invasion</td>
<td>N2 distant abdominal lymph node</td>
</tr>
<tr>
<td>N3 spread to extra-abdominal lymph node</td>
<td></td>
</tr>
<tr>
<td>MX dissemination of lymphoma</td>
<td>MO no evidence of extranodal dissemination</td>
</tr>
<tr>
<td>M1 involvement of other site in gastrointestinal tract</td>
<td></td>
</tr>
</tbody>
</table>
M2 invasion of tissues not contiguous with digestive tract lesion (peritoneum, pleura) or organs (e.g., tonsils, parotid, ocular annexes, lung, liver, breast)
BX bone marrow not explored
B0 no bone marrow involvement
B1 bone marrow infiltration

Annex. III

Radiotherapy for gastric lymphomas: Technique (C.H. Hennequin, J.M. Cosset)

Irradiation technique:
- Patient in supine position
- High-energy photons (>10 MV)
- Minimum three- or four-beam configuration required.
- All beams must be used at each session.
- Treatment requires empty stomach, so treatment must be done away from meals.

Target volumes:
- Total stomach, i.e., from the cardia to and including antrum (gastric lymphomas, in particular those of the MALT marginal zone, which is a multifocal disease [5]).
- Perigastric lymphatic areas

Conformal technique:
- Patient in treatment position
- Scanner: Take slices every 0.5 mm from the lower third of the esophagus to the 3–5 cm under the lower part of the antrum
- Opacify the stomach: a very small amount of contrast liquid (20–30 cc) must be used. A greater quantity leads to increasing the volume of the stomach and therefore overestimation of the target volume.
- GTV (gastric target volume): Stomach from the cardia including all of the antrum
- CTV (clinical target volume): inclusion of perigastric lymph nodes of the lesser curvature (stations 1, 3, and 5) and those of the greater curvature (stations 2, 4, and 6) of the Japanese classification (Marescaux J, Evrard S. EMC techniques chirurgicales-appareil digestif, 1997,40:32–34)
- PTV (planning target volume): 1-cm margin around GTV.
- Critical organs: kidneys, liver. Dose-volume histograms for each of these organs should be done. Usually, the simplest technique that best protects the organs is three beams (one anterior and two lateral). More complex techniques can sometimes be useful, in particular to decrease the irradiated hepatic parenchyma volume.

Doses:
- Low-grade MALT lymphomas: 30 Gy
- High-grade lymphomas (indicated exceptionally): for partial response after chemotherapy: 40 Gy

Fraction:
- 1.8–2 Gy/session; 5 sessions a week
- Prescription of anti-HT3 and proton-pump inhibitors

Annex. IV

Chemotherapy

Different chemotherapies for small B-cell low-grade non-Hodgkin lymphomas

- Alkylating agents
- Chlorambucil (Chloraminophene®): several protocols possible with continuous administration (e.g., 2–3 mg/m²/day) or semicontinuous higher doses e.g., 10–15 mg total dose for 8–15 days once a month for 6 months or 6 mg/m²/day for 14 days/month
- Cyclophosphamide (Endoxan®) 100 mg/day.
- Other protocols including rituximab (Mabthera®) 375 mg/m². Monitor hemogram: white blood cells and platelets for dose adaptation.
REFERENCE CHEMOTHERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMAS (HIGH-GRADE):

CHOP
- Cyclophosphamide 750 mg/m² IV D1
- Doxorubicin 50 mg/m² IV D1
- Vincristine 1.4 mg/m² IV D1
  Do not go beyond 2 mg
- Prednisone 60 mg/m² po D1–D5
  6 cycles repeated every 3 weeks
+/- RITUXIMAB (Mabthera®) 375 mg/m²: perfusion flow adapted to number of courses and to body surface. Administered on D1 with CHOP on D2.

Mini CHOP:
- Cyclophosphamide 600 mg/m² IV D1
- Doxorubicin 25 mg/m² IV D1
- Vincristine 1.4 mg/m² IV D1
  Do not go beyond 2 mg
- Prednisone 60 mg/m² po D1–D5
  6 cycles repeated every 3 weeks

Dose adaptation:
Treatment repeated at full doses if neutrophil >1.5 x 10⁹/l and platelets > 100 x 10⁹/l, if not postpone for 1 or 2 weeks.
If severe neutropenia (<0.5 x 10⁹/l), particularly if complicated by an episode of weakness, use hematopoietic growth factors (G-CSF) and/or dose reduction depending on the context: age, nutritional state, curative or palliative intention.
REFERENCES


