**Gastrointestinal Lymphomas**

ESMO Conference: 11th World Congress on Gastrointestinal Cancer

Bertrand Coiffier

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**WHO classification of B-cell neoplasms**

**Precursor B-cell neoplasms**
- Precursor B-lymphoblastic leukaemia/lymphoma

**Mature (peripheral) B-cell neoplasms**
- B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukaemia
- Plasma cell myeloma/plasmacytoma
- Extramedullary marginal zone B-cell lymphoma (MALT)
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma/Burkitt cell leukaemia

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**MATURE T-CELL AND NK-CELL NEOPLASMS**

- Indolent large granular NK-cell lymphoproliferative disorder
- Aggressive NK/T cell leukaemia/lymphoma
- Adult T-cell leukaemia/lymphoma
- Extramedullary NK/T cell lymphoma, nasal type
- Enteropathy-type intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis Fungoides
- Sézary Syndrome
- Primary cutaneous anaplastic large-cell lymphoma
- Primary cutaneous small/middle CD4 positive T-cell lymphoma
- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative

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**Subtypes and locations**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Stomach</th>
<th>Duodenum</th>
<th>Intestine</th>
<th>Colon</th>
<th>Rectum</th>
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**German multicentre study GIT NHL 01/92**

**Gastric lymphoma (n = 277)**

- Burkitt 33%
- MZCL 40%
- MCL 56%
- DLBCL 56%
- MZCL 40%
- MCL 1%

Koch, J Clin Oncol 2001

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**MALT lymphomas**

- Lymphomas deriving from extranodal organs
- Mucosal organs or non-mucosal organs
- 7–8% of all lymphomas
MALT lymphoma

- Variety of clinical presentations
  - Depending on locations
  - Intestine
  - Lung
  - Skin
  - Thyroid

- Indolent disease
  - B symptoms are uncommon
  - Normal serum LDH and β2 microglobulin

- Disseminated at diagnosis in 1/3 of the patients
  - Multiple involved organs +/- bone marrow (20%)

Sites of presentation

Primary GI manifestations (n = 371)

data of the German multicenter study GIT NHL 01/92

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data of the German multicenter study GIT NHL 01/92

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Primary GI manifestations (n = 371)

data of the German multicenter study GIT NHL 01/92

Different chromosomal translocations
affecting the same signalling pathway in MALT lymphoma

Staging procedures

GI MALT lymphoma

- Endoscopy, multiple biopsies including duodenum
- Endoscopic ultrasound → depth of infiltration perigastric lymph nodes (better than cat scan)
- Helicobacter pylori: biopsy from normal mucosa
- “Double balloon enteroscopy” = “push & pull enteroscopy” → biopsies
- Endoscopy of colon, multiple biopsies
- Campylobacter jejuni (immunoproliferative small intestinal disease = IPSID = sub-type of E-MZCL)
**Gastric MALT Lymphoma: endosonography**

Ultrasound-endoscopy investigation of a MALT patient shows thickening of the wall, with fusion of the normal stratification due to involvement of the mucosa, sub-mucosa and muscularis-mucosa membranes.


**Gastric MALT lymphomas**

- **Recommended staging procedures**
  - According to the clinical symptoms
    - Multifocal disease
    - Dissemination does not change the outcome

**Response to H. pylori eradication**

- Complete remission 81% (n = 96)
- Partial remission 10% (n = 12)
- Non-responder 9% (n = 11)

Duration to 1st CR:
- 59/96 (61%) within 3 months
- 25/96 (26%) within 12 months
- 12/96 (13%) between 12 and 28 months

M Stolte. Gut 2002;50:19

**Response to antibiotics and PPI in stage I gastric MALT lymphoma**

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>staging procedure</th>
<th>CR rate (%)</th>
<th>time to CR (mos.)</th>
<th>relapses (n)</th>
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<td>CT</td>
<td>62</td>
<td>2-34</td>
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Excellent prognosis in non-operated gastric lymphoma

Koch et al., J Clin Oncol 2001;19:3874
Gastric MALT lymphoma
H.p. eradication

Recent data on the long term follow up

Most patients with minimal histological gastric lymphoma residuals remain stable and can be managed safely by a watch and wait strategy

  - median follow up 42 months
  - favourable outcome in 94%
  - minimal residual disease in 62%

  - median follow-up 76 months
  - ~25% had histological score fluctuations and ~13% had stable residual disease
  - 5-year OS is 92%.

Practical Tips for H. pylori eradication

- 2 weeks of triple therapy is the standard regimen
- The choice of the most effective regimen should be based on the prevalence of antibiotic resistance, especially resistance to clarithromycin and metronidazole
- Avoid using clarithromycin-based regimens in patients who have previously been exposed to a macrolide
- Strict adherence to current guidelines significantly reduces treatment failure
- Inform patients that the success of their treatment depends on their adherence to it
- Eradication should be confirmed by the urea breath test after at least 4 weeks post-treatment
- Systematic control for recurrence is unnecessary (annual reinfection rate is low in industrialised countries)

MALT lymphoma Therapy

- Eradication therapy in localized gastric presentation
  - >90% H.Pylori eradication
  - 50-100% histological CR (problems with definition)
- Recurrence (>20%)?
  - problems with definition
  - increasing recurrences with longer follow-up?
- How should we treat persistent or recurrent lymphoma after eradication therapy? (and HP-negative cases?)
- No Consensus on 2nd line Rx

Any role for surgery?

- Several Studies clearly showed that an organ-preserving approach for early gastric lymphoma is not inferior to primary surgery
- Most contemporary treatment algorithms no longer include surgical resection
- Reserve surgery for the management of complications
Gastric MALT lymphoma
Treatment- localised stages

- localised disease
- >80% stages I, II

⇒ radiation therapy!

Gastric MALT lymphoma
Treatment- stages I and II

Radiation Therapy
- Radiotherapy is effective and safe
- It offers the significant advantage of low morbidity compared to surgery
- It represents a curative treatment option for patients H pylori-negative or unresponsive to eradication therapy
- It is probably the best therapy for relapsing patients

Chemotherapy
- For patients with disseminated stage
- For patients with multisite relapses
- For patients not responding to radiotherapy
- For multi relapsing patients
- For patients with transformation

Rituximab activity in MALT lymphoma

34 pts, 11 with previous CT, 15 gastric, 20 stage IV

<table>
<thead>
<tr>
<th>response</th>
<th>n</th>
<th>%</th>
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<tr>
<td>ORR</td>
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<td>73</td>
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<td>SD</td>
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IELSG phase II study, Concorci et al. Blood 2003

International Extranodal Lymphoma Study Group
IELSG-19 ongoing randomized trial

<table>
<thead>
<tr>
<th>Control arm</th>
<th>Chlorambucil (6 mg/m²/d)</th>
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<tr>
<td>weeks</td>
<td>1-6 // 9-10 // 13-14 // 17-18 // 21-22</td>
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<table>
<thead>
<tr>
<th>Study arms</th>
<th>Chlorambucil (6 mg/m²/d)</th>
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<tr>
<td>days</td>
<td>1 8 15 22 42 56 70 84 98 112 126 140 154</td>
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</tbody>
</table>

Rituximab
- 125 mg/m²
- 1 8 15 22 42 56 70 84 98 112 126 140 154
Non-gastric GI MALT lymphoma

Non-gastric GI MALT lymphomas

• Rare, later diagnosis
• No prospective study
• H pylori, Campylobacter jejuni or others
• Try antibiotics first
• Chemotherapy with chlorambucil or rituximab
• So good outcome

Diffuse large B-cell lymphoma

Identical to nodal DLBCL

• Same prognosis
• Same prognostic parameters
• Same chemotherapy: R-CHOP
• Same outcome

• No raison to identify a gastrointestinal subtype in DLBCL

Survival according to IPI score

6696 patients included in GELA randomized studies

Overall survival  Progression-free survival
PFS and OS of 87/93/98 studies

7400 patients 18-80 years old

7 years: PFS = 47.5% [46-49%]; OS = 56% [54.5-57%]

Median follow-up 7 y

R-CHOP: a consistent clinical benefit

Registry data show that these improvements in survival extend to the clinic

R LH 98.5 study: Design

- DLBCL
- Age 60–80 years
- No prior treatment
- PS 0–2
- Stage II–IV

Rituximab: 375 mg/m² on day 1
Cyclophosphamide: 750 mg/m² on day 1
Doxorubicin: 50 mg/m² on day 1
Vincristine: 1.4 mg/m² (up to 2 mg/m²) on day 1
Prednisolone: 40 mg/m²/d days 1–5

MInT study1 British Columbia2

ECOG study3

MInT = MabThera International Trial
ECOG = Eastern Cooperative Oncology Group
TTF = time-to-treatment failure
FFS = failure-free survival


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**Mantle cell lymphoma (MCL)**

- **Morphology:** small to intermediate size lymphoid cells with irregular, cleaved nuclei. Cave: round cell, blastoid and pleomorphic variants.
- **Immunphenotype:** sIg++, l >k , CD19/20/22+, CD5+, CD10-, CD23-, CD11c-, HLA-DR++, CD43+
- **Molecular/cytogenetics:** t(11;14)(q13;q32); overexpression of cyclin D1
- **Clinical outcome:** predominantly elderly, male patients; extranodal involvement, late stage, poor outcome

**Biological risk factors: Cell proliferation I**

... the expression of proliferation signature genes identified patient subsets that differed by more than 5 years in median survival. INK4a/ARF locus deletions dictate tumour proliferation rate and survival.

*Rosenwald, Cancer Cell 2003*

**Biological risk factors: Cell proliferation II**

*Schrader, BJH 2005*
Follicular lymphoma. Rare localization

Primary gastro-intestinal follicular lymphoma

Rare: < 7% primary GI lymphomas
Adult median age 56yrs*  F>M
Small intestine > colon, stomach
(unifocal lesion) (multifocal)
lymphomatous polyposis possible

Hist: FL grade 1, IgH/BCL2 reargt 80%

Clin: COX+ CD10+ BCL6+ Bcl2+ integrin-4α7+ clinical course: indolent, relapses GI, rarely outside origin: local Ag responsive B-cell**

Diff Diag:
- mantle cell lymphoma (lymphomatous polyposis)
- CD20+ CD10+ CD5- cyclinD1+ IgH/BCL1 Reargt
- MALT lymphoma
- CD20+ CD10- BCL6- CD5- cyclin D1- t(11;18) API2/MALT1

* Damaj G et al Ann Oncol 2003 GELA study: 25 cases
** Bende R Am J Pathol 2003, 162:105