Treatment of antibiotic-resistant and non gastric MALT Lymphoma

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MALT Lymphoma: Evidence of antigen-driven growth

- histological features of MALT lymphoma
- somatic hypermutation of immunoglobulin gene (and intraclonal variation)
- association with chronic infectious conditions and auto-immune processes
- therapeutic efficacy of antibiotics

Helicobacter pylori
Infectious etiology of gastric MALT-lymphoma

Different chromosomal translocations affecting the same signalling pathway in MALT lymphoma

- Wyld-type MALT1 synergizes with BCL10 to activate NF-κB
- Rare t(1;14) BCL10 deregulation
- Common t(11;18) API2/MALT1 fusion
- At non-GI sites t(14;18) MALT1 deregulation
- t(3;14) FOXP1 overexpression
- t(5;14) ODZ2 deregulation
- t(9;14) JMJD2C deregulation

NF-κB activation

- Antibiotic-resistant gastric lymphoma
- Poorer outcome and higher risk of histological transformation

A20 (TNFAIP3)
a negative regulator of BCL10-mediated NF-κB activation

Deleted or mutated in up to 40%
Antigen-driven lymphoma development

- *Helicobacter pylori* in gastric MZL
- *Borrelia burgdorferi* in cutaneous MZL
- *Chlamydophila psittaci* in some OALs
- *Campylobacter jejuni* in IPSID
- *HCV* association with some non-MALT MZL
- *Achromobacter (Alcaligenes) Xylosoxidans* in BALT-Lymphoma
Most gastric MALT lymphomas regress after *H. pylori* eradication

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>CR rate (%)</th>
<th>Time to CR (mos.)</th>
<th>Relapses (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savio, 1996</td>
<td>12</td>
<td>84</td>
<td>2-4</td>
<td>0</td>
</tr>
<tr>
<td>Pinotti, 1997</td>
<td>45</td>
<td>67</td>
<td>3-18</td>
<td>2</td>
</tr>
<tr>
<td>Neubauer, 1997</td>
<td>50</td>
<td>80</td>
<td>1-9</td>
<td>5</td>
</tr>
<tr>
<td>Nobre Leitao, 1998</td>
<td>17</td>
<td>100</td>
<td>1-12</td>
<td>1</td>
</tr>
<tr>
<td>Steinbach, 1999</td>
<td>23</td>
<td>56</td>
<td>3-45</td>
<td>0</td>
</tr>
<tr>
<td>Montalban, 2001</td>
<td>19</td>
<td>95</td>
<td>2-19</td>
<td>0</td>
</tr>
<tr>
<td>Ruskone-Formestraux, 2001</td>
<td>24</td>
<td>79</td>
<td>2-18</td>
<td>2</td>
</tr>
<tr>
<td>Bertoni, 2002</td>
<td></td>
<td>62</td>
<td>3-24</td>
<td>15</td>
</tr>
<tr>
<td>Zullo, 2010 (meta-analysis)</td>
<td>1408</td>
<td>77.5</td>
<td>5 (median)</td>
<td>72/994</td>
</tr>
</tbody>
</table>
Decreasing incidence of gastric MALT lymphomas in the era of anti-*Helicobacter pylori* interventions: results from a population-based study on extranodal marginal zone lymphomas

S. Luminari et al. *Ann Oncol* 2010

<table>
<thead>
<tr>
<th>Prevalence of HP+ MALT lymphoma cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-2001</td>
</tr>
<tr>
<td>2002-2007</td>
</tr>
</tbody>
</table>

Reduction of 46% in the UK (London area)

<table>
<thead>
<tr>
<th>Wotherspoon et al, Lancet 1991:</th>
<th>92% prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-2013:</td>
<td>50% prevalence</td>
</tr>
</tbody>
</table>

A. Wotherspoon, personal communication, 2014
MALT Lymphoma

- Gastrointestinal tract 50%
  - Stomach 34%
  - intestine (inc IPSID) 5-8%
- Salivary gland 26%
- Respiratory tract
  - Lung 9%
  - pharynx, larynx, trachea
- Thyroid 4-6%
- Ocular adnexa 10-17%
  - conjunctiva
  - lacrimal gland
  - orbit*
- Thymus
- Liver 3%
- Genitourinary tract 3%
  - bladder
  - prostate
  - kidney
- Breast 3%
- Skin* 10-12%
- Dura*
- Rare sites

*not mucosal

Zucca et al. 2003, Thieblement & Coiffier 2004
Staging of MALT Lymphoma

- multifocal disease in $\geq 25\%$ of cases
- PET use is controversial and has uncertain clinical utility (*ESMO Guidelines*)
- variable FDG-avidity (higher in non-gastric lesions)
- pooled PET/CT detection rate, 71% (95% CI: 61-80%) in a literature meta-analysis

Treglia et al. Hematol Oncol. 2014
How to treat antibiotic-resistant and non-gastric MALT Lymphoma?

How to treat advanced stages?
CagA might function as a bacterium-derived oncoprotein in the carcinogenesis of gastric MALT lymphoma.

CagA undergoes tyrosine phosphorylation in tumor B-cells.

CagA upregulates Bcl-2 and Bcl-XL expression, which prevents apoptosis.

CagA activates extracellular signal-regulated kinase and p38 mitogen-activated PK.

Antibiotic therapy in non-gastric MALT lymphomas: which evidence

<table>
<thead>
<tr>
<th>Involved Organ</th>
<th>Targeted Pathogen</th>
<th>Antibiotic Regimen</th>
<th>No. of Patients</th>
<th>Type of Study</th>
<th>Overall Lymphoma Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular adnexa</td>
<td><em>C. psittaci</em></td>
<td>Doxycycline, 100 mg bid × 21 d</td>
<td>120</td>
<td>2 Prospective, 4 Retrospective, 1 Case report</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clarithromycin, 500 mg bid × 6 mos</td>
<td>11</td>
<td>Prospective</td>
<td>45%</td>
</tr>
<tr>
<td>Skin</td>
<td><em>B. burgdorferi</em></td>
<td>Ceftriaxone, 2 g/d × 14 d (in most cases)</td>
<td>5</td>
<td>Case reports</td>
<td>40%</td>
</tr>
</tbody>
</table>

Why to treat HP-negative patients with antibiotics?

- False negative diagnostic test
- Other microorganisms involved (*H. heilmannii*)
- Responses in 14 of 72 published cases (19%)

**EGILS Consensus Report:** Ruskone Formestraux et al. Gut 2011; 60:747
How to predict H pylori–dependence of early-stage gastric MALT lymphoma?

<table>
<thead>
<tr>
<th>Response to HP eradication</th>
<th>Markers</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HP dependence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costimulatory molecules</td>
<td>CD86 (B7.2)</td>
<td>IHC</td>
</tr>
<tr>
<td>CD4⁺CD56⁺ Treg</td>
<td>FOXP3</td>
<td>IHC</td>
</tr>
<tr>
<td>Methylation</td>
<td>p16INK4A</td>
<td>Methylation-specific PCR</td>
</tr>
<tr>
<td>HP-specific protein</td>
<td>CagA protein</td>
<td>IHC</td>
</tr>
<tr>
<td>HP-specific protein</td>
<td>Serum CagA IgG antibody</td>
<td>ELISA (CagA kit)</td>
</tr>
<tr>
<td><strong>HP independence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome</td>
<td>t(11;18)(p21;q21)</td>
<td>RT-PCR or FISH</td>
</tr>
<tr>
<td>Chromosome</td>
<td>t(1;14)(p22;q32)</td>
<td>FISH</td>
</tr>
<tr>
<td>Protein</td>
<td>BCL10 nuclear expression</td>
<td>IHC</td>
</tr>
<tr>
<td>Chemokine/chemokine receptor</td>
<td>CXCR3</td>
<td>IHC</td>
</tr>
<tr>
<td>Methylation</td>
<td>MAD2</td>
<td>Methylation-specific PCR</td>
</tr>
<tr>
<td>mRNA</td>
<td>E2A</td>
<td>miRNAs RT–PCR</td>
</tr>
<tr>
<td>mRNA</td>
<td>miR-203</td>
<td>miRNAs RT–PCR</td>
</tr>
<tr>
<td>mRNA</td>
<td>miR-142-5p and miR-155</td>
<td>miRNAs RT–PCR</td>
</tr>
</tbody>
</table>

Treatment of gastric MALT lymphoma

*HP* eradication is the standard initial therapy for *HP*-positive localized disease

... but several issues remain unsettled:

- evaluation of responses
- treatment of residual disease
- follow up policies following antibiotics
- Treatment of *H. pylori*-negative cases
- antibiotics in *H. pylori*-positive DLBCL cases?
Same outcome after different treatments in stage IE gastric MALT lymphoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N° of pts</th>
<th>CR rate</th>
<th>5-years OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>45</td>
<td>67%</td>
<td>94% (65-99)</td>
</tr>
<tr>
<td>Local treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14</td>
<td>100%</td>
<td>92% (57-99)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>8</td>
<td>50%</td>
<td>75% (32-93)</td>
</tr>
<tr>
<td>Combined modality&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
<td>100%</td>
<td>80% (20-97)</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>74%</td>
<td>89% (76-96)</td>
</tr>
</tbody>
</table>

<sup>a</sup> surgery ± RT
<sup>b</sup> surgery + adjuvant chemotherapy

*Pinotti et al, Leuk Lymphoma 1997*
Radiotherapy in gastric MALT lymphoma

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>RT dose (Gy)</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schechter, 1998</td>
<td>17</td>
<td>28-43</td>
<td>100% at 2 yr</td>
</tr>
<tr>
<td>Tsang, 2001</td>
<td>9</td>
<td>20-30</td>
<td>100% at 5 yr</td>
</tr>
<tr>
<td>Yahalom, 2002</td>
<td>51</td>
<td>30 median</td>
<td>89% at 4 yr</td>
</tr>
<tr>
<td>Hitchcock, 2002</td>
<td>9</td>
<td>34 median</td>
<td>78% (100% local)</td>
</tr>
</tbody>
</table>

- optimal RT volume, dose and technique?
- does this really translate to cure?
- in a very indolent condition, is the potential toxicity acceptable?
- long term safety? (malignancy, gastric and renal toxicity)

RT Toxicity can be reduced using modern 3D techniques and minimizing the RT dose to the kidneys and the liver.

excellent local control in non-gastric sites, too!
Radiotherapy in gastric MALT lymphoma

102 eligible pts, 58 untreated. RT fields included stomach/involved nodes in 61 patients and whole abdomen in 41.

Risk factors for TF: large-cell component and exophytic growth pattern.

RT field size, RT dose not associated with TF.

Wirth et al. Ann Oncol 2013

Long-term outcome for gastric marginal zone lymphoma treated with radiotherapy: a retrospective, multi-centre, International Extranodal Lymphoma Study Group study

Rituximab activity in MALT lymphoma

<table>
<thead>
<tr>
<th>response n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>25 73</td>
</tr>
<tr>
<td>SD</td>
<td>6 18</td>
</tr>
<tr>
<td>PD</td>
<td>3 9</td>
</tr>
</tbody>
</table>

34 pts, 11 with prior chemotherapy, 15 gastric, 20 stage IV

IELSG phase II study, Conconi et al. Blood 2003
## Chemotherapy in MALT lymphomas

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nr. pts</th>
<th>ORR</th>
<th>CR</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylators</td>
<td>24 pts</td>
<td>100%</td>
<td>75%</td>
<td>Hammel P. J Clin Oncol 1995</td>
</tr>
<tr>
<td>R-CHOP/CNOP</td>
<td>7 pts</td>
<td>100%</td>
<td>100%</td>
<td>Raderer M. Ann Oncol 2002</td>
</tr>
<tr>
<td>Cladribine</td>
<td>26 pts</td>
<td>100%</td>
<td>84%</td>
<td>Jäger G. J Clin Oncol 2002</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>16 pts</td>
<td>93%</td>
<td>56%</td>
<td>Raderer M. J Clin Oncol 2005</td>
</tr>
<tr>
<td>Fluda-Mito</td>
<td>20 pts</td>
<td>100%</td>
<td>100%</td>
<td>Zinzani PL. Cancer 2004</td>
</tr>
<tr>
<td>R-cladribine</td>
<td>39 pts</td>
<td>81%</td>
<td>58%</td>
<td>Troch M. Haematologica 2013</td>
</tr>
</tbody>
</table>
Final Trial Profile

International Extranodal Lymphoma Study Group - IELSG 19 Randomised Study

Randomisation 1:1:6

Chl  R-Chl  R

Restaging

SD - PR - CR

Chl  R-Chl  R

N= 450

Strata
- IPI (lo/lo-int vs. int-hi/hi)
- nodal involvement (yes vs. no)
- site (gastric vs. non-gastric)
- prior local treatment (yes vs. no)

Main Endpoint, EFS

E. Zucca, 12-ICML, Hematol Oncol 2013. 31(suppl 1):97. Abs 007
Event-Free Survival

International Extranodal Lymphoma Study Group - IELSG 19 Randomised Study

**5-year EFS (95% CI):**
- Chlorambucil, 52% (42%-60%)
- R-Chlorambucil, 70% (61%-77%)
- Rituximab, 51% (40%-61%)

**Log-rank HR 95% C.I.**
- R vs. Chl, $P=0.957$, HR 0.99 (0.82-1.20)
- R-Chl vs. Chl, $P=0.0005$, HR 0.52 (0.35-0.75)
- R-Chl vs. R, $P=0.0015$, HR 0.51 (0.33-0.78)

**Number at risk**
- Chlorambucil 130, 99, 84, 75, 62, 55
- R-Chlorambucil 131, 113, 107, 96, 85, 74
- Rituximab 132, 100, 77, 52, 36, 10

International Extranodal Lymphoma Study Group - IELSG 19 Randomised Study

Overall Survival

- **Chlorambucil**: 89% (82%-94%)
- **R-Chlorambucil**: 89% (82%-94%)
- **Rituximab**: 94% (86%-97%)

MALT-2008-01 Study

Event Free Survival

The large majority of patients required only 4 cycles

Median follow-up: 27 months (6-40 months)

A. Salar, 12-ICML, Hematol Oncol 2013. 31(suppl 1):129-130. Abs 100
Chemotherapy in MALT lymphoma

- Only one randomised trial: R-Chlorambucil better than Chlorambucil alone
  
  (Zucca 2013)

- Single alkylating agents: 100% ORR (75%CR)

  (Hammel 1995)

- Cladribine: higher CR rate in gastric than extragastric (but risk of secondary MDS)

  (Jaeger 2002 and 2006)

- Chlorambucil plus Mitoxantrone and Prednisone as well as Fludarabine in combination with Mitoxantrone and the classic CVP are active and well-tolerated regimens

  (Wohrer 2003; Zinzani 2004)

- Aggressive anthracycline-containing regimens to be reserved for cases with transformation or bulky masses

  (Thieblemont 2005)

- Bendamustine combinations currently under investigation

  (Salar, submitted to 12-ICML)
NFkB - targeted Therapies?

IELSG-25 and Austrian phase II trials of bortezomib for MALT Lymphoma

- 1.3 mg/m² days 1,4,8,11 q21
- 21 pts with R/R MALT lymphoma,
- 52% stage IV
- 52% primary gastric
- median follow up 17 mos
- CR 27%, PR 37%
- Toxicity similar to that observed in multiple myeloma and other NHL (peripheral neuropathy and fatigue)
- 3 deaths, non-related to treatment, observed during the early follow up.

Conconi et al. Ann Oncol 2010

- 1.5 mg/m² days 1,4,8,11 q21
- 16 pts front-line, 4 primary gastric
- median follow up 23 mos
- ORR 80%, CR 43%
- Fifteen patients required dose reductions due to either neuropathy (7 patients) or diarrhea (8 patients).

Trosch et al. Haematologica 2010
Phase II study of bortezomib in relapsed/refractory MALT lymphomas

Conconi A Ann Oncol 2011

Progression free survival

Median PFS: 25 months (range, 1–47 months)

<table>
<thead>
<tr>
<th>Interval</th>
<th>Entered</th>
<th>Relapsed</th>
<th>Censored</th>
<th>Survival</th>
<th>[95% Conf. Int.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1 yr</td>
<td>31</td>
<td>10</td>
<td>7</td>
<td>0.64</td>
<td>0.43 - 0.79</td>
</tr>
<tr>
<td>1 - 2 yr</td>
<td>14</td>
<td>2</td>
<td>4</td>
<td>0.53</td>
<td>0.32 - 0.71</td>
</tr>
<tr>
<td>2 - 3 yr</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0.32</td>
<td>0.12 - 0.54</td>
</tr>
<tr>
<td>3 - 4 yr</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0.32</td>
<td>0.12 - 0.54</td>
</tr>
</tbody>
</table>
Everolimus in relapsed/refractory MZL

Intent to treat analysis on all enrolled patients

Progression free survival

median PFS: 14 months

Conconi A. Br J Haematol. 2014 Jul;166(1):69-76
Lenalidomide in MALT lymphomas

Lenalidomide 25 mg/d  d1-21,  q28 d
18 patients  (5 gastric , 13 extragastric MALT)

**ORR 61% (11/18)**
- 6 CR
- 5 PR
- 3 SD
- 2 PD
- 2 withdrawals

Manageable toxicity including neutropenia ( G3 in 3 pts)

Kiesewetter B. Haematologica 2012
# R-Lenalidomide in MZL: Response Rates and PFS

<table>
<thead>
<tr>
<th>n (%)</th>
<th>SLL (N=30)</th>
<th>MZL (N=27)*</th>
<th>FL (N=46)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>24 (80)</td>
<td>24(89)</td>
<td>45(98)</td>
</tr>
<tr>
<td>CR/Cru</td>
<td>8(27)</td>
<td>18(67)</td>
<td>40(87)</td>
</tr>
<tr>
<td>PR</td>
<td>16(53)</td>
<td>6(22)</td>
<td>5(11)</td>
</tr>
<tr>
<td>SD</td>
<td>4(13)</td>
<td>3(11)</td>
<td>1(2)</td>
</tr>
<tr>
<td>PD</td>
<td>2(7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*7 pts not evaluable for response:
- 5 due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

MZL – Nodal and Extranodal

G.S. Nowakowski. 12- ICML, Lugano 2013
PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

Phase-2 studies in preparation for R/R MZL

- Idelalisib + Obinotumumab
- Lenalidomide + Chloritromycin

both will start in 2015

ielsg@ticino.com
Treatment of patients who failed antibiotics and nongastric cases

• Involved-field radiotherapy:
  - 30 to 40 Gy in 15-20 fractions using modern radiation techniques
  - lack of prospective studies

• Chemotherapy and/or immunotherapy:
  - Chemotherapy and Rituximab are effective in patients with MALT lymphoma of all stages

• Both radiotherapy and chemotherapy seems to have a similar therapeutic potential, there is no definitive evidence in favour of one modality

• Surgery restricted to the treatment of complications

• If clinical trials are available, patients should be included

13-ICML
13th International Conference on Malignant Lymphoma

Palazzo dei Congressi
Lugano (Switzerland)
www.lymphcon.ch

SAVE THE DATE: June 17-20, 2015