Potential applications of FDG-PET in Mantle Cell Lymphoma

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And
Prof. Le Gouill Steven

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NHLs

- Follicular Lymphoma: 22%
- DLBCL: 35%
- MALT: 8%
- MZL: 3%
- SLL: 8%
- MCL: 6%
- Anaplastic T/nul: 2%
- PTCL-NOS: 7%
- Lymphoblastiques: 2%
- Burkitt: 1%
- Other: 6%

Adapted from R Gressin
Küppers R. Nature reviews cancer 2005 p251

VDJ

Clonal expansion
Somatic Hypermutation
Class switch recombination

Differenciation

B cell

BCR/Ag

BCR+/-

apoptosis

Germinal center

Marginal zone

Mantle

Plasmablast

Plasma cells

Long live plasma cell

Memory

B-cell

Ag selection

Clonal expansion
Somatic Hypermutation
Class switch recombination

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Long live plasma cell

Memory

B-cell

Ag selection
FISH

*Immunochemistry*

Overexpression of cycline D1 (CCND1)
Dysregulation of cell cycle in MCL cells

- Abnormal mitotic signals
- Lost of « checkpoints »
- Dysregulation of proliferation
- Chromosomic instability
- Genomic instability

Adapted from Malumbres et al. Nature reviews cancer 2009 p153
CHALLENGES IN MCL DURING THE LAST DECADE:

• How to improve response rates?
• How to reach long term CR?
MCL younger: Randomization and Treatment

4 x R-CHOP
2 x R-CHOP

DexaBEAM (stem cell mobilization)

Cyclo 120mg/kg + TBI 12 Gray

PBSCT

PR, CR

(2+1) x R-CHOP/R-DHAP alternating
stem cell mobilization after course 6

PR, CR

TBI 10 Gray
Ara-C 4x1.5 g/m2
Melphalan 140 mg/m2

PBSCT

Adapted from O Hermine ASH 2010 Abstract 110
MCL Younger: Duration of CR after ASCT

median follow-up = 30
R-DHAP, median not reached
R-CHOP, median not reached
p = 0.0485

numbers at risk
R-DHAP  74  55  40  24  11  0
R-CHOP  79  54  38  25  13  0
First RCT for MCL Elderly
8 countries, n = 560 (Jan 2004-Oct 2010)

Newly diagnosed, >60-65 yr; performance 0-2, Stages II-IV, central PA review

- 8 x R-CHOP
- IFN-\(\alpha\) maintenance (3 x 3 M IU/week) or Peg-IFN (1ug/kg week)
- CR, CRu, PR

- 6 x R-FC
- Rituximab maintenance (all 2 months)

KLUIJN-NELEMANS ET AL NEJM
MCL Elderly: overall survival related to induction regimen

After R-CHOP

- Median follow-up = 38 months
- R, median not reached (p = 0.0061)

<table>
<thead>
<tr>
<th>Numbers at Risk</th>
<th>Months Since Start of Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>74 70 53 34 19 8 2 0</td>
</tr>
<tr>
<td>IFN</td>
<td>76 72 49 31 13 7 1 0</td>
</tr>
</tbody>
</table>

After R-FC

- Median follow-up = 35 months
- R, median = 82 months
- IFN, median not reached (p = 0.41)

<table>
<thead>
<tr>
<th>Numbers at Risk</th>
<th>Months Since Start of Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>54 48 30 18 11 4 2 0</td>
</tr>
<tr>
<td>IFN</td>
<td>44 42 29 16 11 6 2 0</td>
</tr>
</tbody>
</table>

p = 0.055 for interaction of induction and maintenance
CHALLENGES OF THE LAST DECADES IN MCL:

• How to improve response rates?
  – By the Use of high-dose aracytine upfront for young patients

• How to reach long term CR?
  – By the use of Rituximab maintenance for elderly patients

WHAT NEXT? …. New molecules: velcade, temsirolimus, lenalidomide, GA-101, BTK inhibitors ..
NEW CHALLENGES IN MCL:
How to identify high- or low-risk patients in order to build a risk-tailored therapy?

• Biomarkers at time of diagnosis (MIPI, Ki67, cytogenetic abnormalities, epigenetic dysregulations …)

• How to use MRD?

• How to use FDG-PET?
**STATE OF ART ........**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Pretreatment</th>
<th>Mid-Treatment</th>
<th>Response Assessment</th>
<th>Post-Treatment Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely FDG avid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>Yes*</td>
<td>Clinical trial</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HL</td>
<td>Yes*</td>
<td>Clinical trial</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Follicular NHLs</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not</td>
<td>No</td>
</tr>
<tr>
<td>MCL</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not</td>
<td>No</td>
</tr>
<tr>
<td>Variably FDG avid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other aggressive NHLs</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not*†</td>
<td>No</td>
</tr>
<tr>
<td>Other indolent NHLs</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not†</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: PET, positron emission tomography; CT, computed tomography; FDG, \(^{18}\)F-fluorodeoxyglucose; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MCL, mantle-cell lymphoma; ORR, overall response rate; CR, complete remission.

*Recommended but not required pretreatment.
†Recommended only if CR/PR is a primary study end point.
‡Recommended only if PET is positive pretreatment.
However, FDG-PET is moving forward in MCL:

• STEP 1: FDG-PET at diagnosis?
• STEP 2: FDG-PET for response assessment at end of therapy?
• STEP 3: FDG-PET for mid-treatment response assessment?
### STEP 1: FDG-PET at diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sensitivity</th>
<th>SUVmax range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elstrom Blood 2003</td>
<td>7</td>
<td>100%</td>
<td>Not performed</td>
</tr>
<tr>
<td>Brepoels Leukemia &amp; lymphoma 2008</td>
<td>37</td>
<td>100%</td>
<td>~1.8-19</td>
</tr>
<tr>
<td>Karam Nuclear medicine communications 2009</td>
<td>81</td>
<td>100%</td>
<td>&lt; ou = 5: n=20</td>
</tr>
<tr>
<td>Gill Clinical Lymphoma &amp; Myeloma 2008</td>
<td>28</td>
<td>100%</td>
<td>Not performed</td>
</tr>
<tr>
<td>Schaffel Blood (ASH Annual Meeting Abstracts) 2009</td>
<td>75</td>
<td>95%</td>
<td>Not performed</td>
</tr>
<tr>
<td>Bodet-milin Eur journal of nuclear medicine 2010</td>
<td>44</td>
<td>100%</td>
<td>1.7-18.8</td>
</tr>
<tr>
<td>Alavi Clinical Lymphoma &amp; Myeloma 2011</td>
<td>19</td>
<td>100%</td>
<td>Not performed</td>
</tr>
<tr>
<td>Hosein Am journal of hematology 2011</td>
<td>34</td>
<td>94%</td>
<td>1.6-14</td>
</tr>
<tr>
<td>Mato Cancer 2012</td>
<td>53</td>
<td>92%</td>
<td>2.5-36.7</td>
</tr>
</tbody>
</table>

- High sensitivity for nodes and spleen.
- Insufficient sensitivity for bone marrow and gastrointestinal involvement.
- Heterogeneous Suvmax
STEP 1

SUV max value

KI67 + cells

t(11:14) ONCOGENIC events (P53, MYC, ATM, BCL-2...)

Naive B cell Early MCL Classical MCL Blastoid MCL
No link between SUVmax and histologic subtype

Bodet-milin et al (Eur journal of nuclear medicine 2010)

No link between SUVmax and proliferation
STEP 1

Prognosis Index?

Bodet-milin et al (Eur journal of nuclear medicine 2010)
• STEP 1: FDG-PET at diagnosis OK
• STEP 2: FDG-PET for response assessment at end of therapy
• STEP 3: FDG-PET for mid-treatment response assessment
## Steps 2: Response assessment by PET

<table>
<thead>
<tr>
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<th>N</th>
<th>Treatment</th>
<th>Interim PET evaluation</th>
<th>End treatment PET evaluation</th>
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<tr>
<td>Brepoels Leukemia &amp; lymphoma 2008</td>
<td>37</td>
<td>Frontline Heterogeneous</td>
<td>Eortc + IHP criteria</td>
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<tr>
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<td>Frontline 4 RCHOP 14 2-3 RICE + ASCT</td>
<td>IHP criteria</td>
<td>Not performed</td>
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<tr>
<td>Mato Cancer 2012</td>
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<td>Frontline R-HyperCVAD</td>
<td>IHP criteria</td>
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</tr>
</tbody>
</table>
STEP 2: FDG-PET for response assessment at end of therapy

Brepoels, leukemia and lymphoma 2008

Mato et al. Cancer 2012

Bodet-Milin et al. Eur journal of nuclear medicine 2010
• **STEP 1:** FDG-PET at diagnosis **OK**
• **STEP 2:** FDG-PET for response assessment at end of therapy **Probably yes but need to be validated**
• **STEP 3:** FDG-PET for mid-treatment response assessment
STEP 3: FDG-PET for mid-treatment response assessment

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- In all studies, PET seems to be able to identify non responders after 2 or 3 cycles of chemotherapy, especially in patients considered as responders on CT

- **But** Negative interim PET is associated with better PFS (84% vs 40%) and OS (94% vs 70%) in only ¼ study (Schaffel et al.)
However, Art is moving forward!

- **STEP 1:** FDG-PET at diagnosis OK
- **STEP 2:** FDG-PET for response assessment at end of therapy *Probably but need to be validated*
- **STEP 3:** FDG-PET for mid-treatment response assessment *Uncertain and need prospective studies*
Arm A
Observation
every 2 months for 3 yrs

Arm B
Maintenance R (375mg/m²)
every 2 months for 3 yrs

R-DHAP* or R-DHA-Carboplatin or R-DHA-Oxaliplatin
Risk-adapted treatment

At time of diagnosis:
- MIPI
- Ki67
- Cytogenetic abnormalities
- FDG-PET SUV index ?

At mid-term:
- MRD measurement
- FDG-PET response ?

At end of treatment:
- MRD level
- FDG-PET response ?
THANKS / MERCI

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