La TEP dans le lymphome
Impacts cliniques en 2017

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Incidence and Anatomic Regions Detected by FDG PET Relation to Histologic Types According to World Health Organization Classification

<table>
<thead>
<tr>
<th>Histology</th>
<th>Total no. (%)</th>
<th>Head and neck</th>
<th>Chest</th>
<th>Abdomen</th>
<th>Pelvis</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALC1</td>
<td>25/25 (100)</td>
<td>9/9</td>
<td>3/3</td>
<td>3/3</td>
<td>2/2</td>
<td>8/8</td>
</tr>
<tr>
<td>AITL</td>
<td>34/34 (100)</td>
<td>12/12</td>
<td>8/8</td>
<td>10/10</td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td>NK/T-nasal</td>
<td>30/30 (100)</td>
<td>9/9</td>
<td>6/6</td>
<td>5/5</td>
<td>1/1</td>
<td>9/9</td>
</tr>
<tr>
<td>PTCL</td>
<td>54/55 (98)</td>
<td>20/20</td>
<td>10/11</td>
<td>9/9</td>
<td>6/6</td>
<td>9/9</td>
</tr>
<tr>
<td>Burkitt</td>
<td>21/21 (100)</td>
<td>2/2</td>
<td>6/6</td>
<td>5/5</td>
<td>3/3</td>
<td>5/5</td>
</tr>
<tr>
<td>DLBCL</td>
<td>268/276 (97)</td>
<td>79/81</td>
<td>41/43</td>
<td>60/61</td>
<td>28/28</td>
<td>60/63*</td>
</tr>
<tr>
<td>FL</td>
<td>175/193 (91)</td>
<td>55/58</td>
<td>38/43</td>
<td>34/39</td>
<td>40/42</td>
<td>8/11†</td>
</tr>
<tr>
<td>MALT‡</td>
<td>89/109 (82)</td>
<td>28/30</td>
<td>16/19</td>
<td>10/11</td>
<td>5/7</td>
<td>30/42§</td>
</tr>
<tr>
<td>SMZL</td>
<td>10/19 (53)</td>
<td>2/3</td>
<td>1/2</td>
<td>4/9</td>
<td>3/5</td>
<td>0/0</td>
</tr>
<tr>
<td>MCL</td>
<td>51/51 (100)</td>
<td>23/23</td>
<td>9/9</td>
<td>6/6</td>
<td>9/9</td>
<td>4/4</td>
</tr>
<tr>
<td>SL</td>
<td>9/18 (50)</td>
<td>3/6</td>
<td>4/5</td>
<td>2/4</td>
<td>0/3</td>
<td>0/0</td>
</tr>
<tr>
<td>HL</td>
<td>73/75 (97)</td>
<td>31/31</td>
<td>23/24</td>
<td>11/12</td>
<td>2/2</td>
<td>6/6</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panniculitis-like T</td>
<td>5/7 (71)</td>
<td>0/0</td>
<td>0/2</td>
<td>0/0</td>
<td>2/2</td>
<td>3/3</td>
</tr>
<tr>
<td>Total no. (%)</td>
<td>844/913 (92.4)</td>
<td>273/284 (96.1)</td>
<td>165/181 (91.2)</td>
<td>159/174 (91.4)</td>
<td>103/112 (92.8)</td>
<td>144/162 (88.9)</td>
</tr>
</tbody>
</table>

Maximum Standardized Uptake Value in Four Types of Lymphoma

<table>
<thead>
<tr>
<th>Histology</th>
<th>Median SUV max</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK/T-cell lymphoma</td>
<td>9.4</td>
</tr>
<tr>
<td>DLBCL</td>
<td>9.9</td>
</tr>
<tr>
<td>Indolent B-cell lymphoma</td>
<td>3.3*</td>
</tr>
<tr>
<td>HL</td>
<td>6.6*</td>
</tr>
</tbody>
</table>

Tsukamoto et al Cancer 2007; 110: 652
Why using PET in curable lymphoma?

• We need
  • a precise determination of initial disease extent
  • knowledge about prognostic and predictive factors
  • accurate and early assessment of responsiveness to therapy

• In order to
  • Improve the cure rates in patients with risk factors
  • Reduce toxicity of treatment
  • Optimize the balance between the risk of overtreatment and undertreatment

PET can satisfy some of these needs
Staging / Response assessment / Prognosis
Impact de la réponse intérimaire
Interim PET

• Much more than CT which measures the tumor size, functionnal imaging which evaluates the activity of the tumor cells appears to be more relevant for early response assessment

• PET allows analyzing during treatment a continuous metabolic process
  • PET after 1 or 2 cycles:
    • Analyses the response of cells with the highest level of proliferation
    • Identifies early responding patients (chemosensitivity)
    • A negative PET is not required
  
  • PET after 3 to 4 cycles:
    • Allows identifying tumor re-growth
    • Identifies late responding patients

Y Kasamon et al, Curr Opin Oncol 2008; 20: 206
Adapter le traitement selon la réponse intérimaire

• Désescalader le traitement des patients chimiosensibles (iPET-): limiter la toxicité à long terme avec un contrôle tumoral identique

• Escalader le traitement des patients répondeurs lents (iPET+): réverser le pronostic péjoratif des iPET+
Prognosis value of early PET interpreted according to 5PS in HL

Gallamini A, JCO 2007; 25: 3746

Biggi, JNM 2013

Rossi, JNM 2014

VPP = 50 - 55%
VPN = 80 - 90%
Peut-on se passer de la radiothérapie?

### EORTC/LYSA

<table>
<thead>
<tr>
<th>Médiastin/Thorax &gt; 0.35</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 4 aires ganglionnaires</td>
</tr>
<tr>
<td>B et VS ≥ 30 ou A et VS ≥ 50</td>
</tr>
<tr>
<td>Age ≥ 50</td>
</tr>
</tbody>
</table>

### H10F

<table>
<thead>
<tr>
<th>2 ABVD</th>
<th>PET</th>
<th>1 ABVD+IN-RT 30 Gy (+6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2 ABVD</th>
<th>-</th>
<th>2 ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### H10U

<table>
<thead>
<tr>
<th>2 ABVD</th>
<th>PET</th>
<th>2 ABVD+IN-RT 30 Gy (+6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2 ABVD</th>
<th>-</th>
<th>4 ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PET2- = 83% (465/562)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PET2- = 70% (594/858)</th>
</tr>
</thead>
</table>
PET negative group: no INRT vs. ABVD+INRT

FAVORABLE: PFS

HR (95% CI) = 15.8 (3.8, 66.1)
Non-inferiority p=0.986
5 yr PFS 87% vs. 99%

HR: Hazard Ratio ABVD no INRT vs. ABVD+INRT

M. André, JCO 2017
PET negative group: no INRT vs. ABVD+INRT
UNFAVORABLE: PFS

HR (95% CI) = 1.5 (0.8, 2.5)
Non-inferiority p=0.908
5 yr PFS 89% vs. 92%

M. André, JCO 2017
Doit on escalader les TEP2+?

H10F

2 ABVD

PET

1 ABVD+IN-RT 30 Gy (+6)

H10U

2 ABVD

PET

2 ABVD+IN-RT 30 Gy (+6)

2 BEACOPPesc+IN-RT 30 (+6)
H10 trial: outcome of PET2 positive patients according to treatment arm

**A**
Progression-Free Survival

- BEACOPP
- ABVD

P = 0.002, HR = 0.42 (95% CI = 0.23 to 0.74)

**B**
Overall Survival

- BEACOPP
- ABVD

P = 0.062, HR = 0.45 (95% CI = 0.19 to 1.07)
BEACOPP vs ABVD in advanced HL

Stage IIIB-IV

BEACOPP [esc x 4 + Baseline x 4] vs ABVD x 6/8

Median FU = 61 months

PFS

Hazard ratio, 0.45
P = 0.004

P = 0.004

OS

Hazard ratio, 0.75
P = 0.39

P = 0.39

Viviani S, NEJM 2011; 365: 203
BEACOPPesc: toxicité long terme

- Infertilité  
  Behringer K, JCO, 2013
  Aménorrhée 4 ans après fin Chimio
  6-8 BEACOPPesc
  2 BEACOPPesc + 2 ABVD
  ou 4 ABVD

- LAM / MDS secondaires
  Engert A, JCO 2009
AHL 2011

Non inferiority of the experimental arm
Standard arm : 85% 5y-PFS ;
Experimental arm: 5y-PFS > 75% (HR=1.77)
AHL2011: PET2 results (central review)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Standard</th>
<th>Experimental</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 401</td>
<td>n = 381</td>
<td>n = 782</td>
</tr>
<tr>
<td>PET2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable</td>
<td>386</td>
<td>368</td>
<td>754</td>
</tr>
<tr>
<td></td>
<td>96%</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>Negative</td>
<td>338</td>
<td>319</td>
<td>657</td>
</tr>
<tr>
<td></td>
<td>88%</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td>Positive</td>
<td>48</td>
<td>49</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>

In an intent to treat basis, 84% of patients received 2 x BEACOPPesc + 4 x ABVD in the experimental arm.

Casasnovas RO, ASH 2015; Abs 577
AHL 2011: PFS according to treatment arm

Median follow-up = 16.3 months (0.1 – 37.4)

2y-PFS = 91.6%
2y-PFS = 88.3%

p = 0.79 ; HR = 0.817 (95% CI 0.499 - 1.337)

Casasnovas RO, ASH 2015; Abs 577
AHL2011: interim PET results (central review)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Standard</th>
<th></th>
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<th></th>
<th>All</th>
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<tbody>
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<td><strong>PET2</strong></td>
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<td>657</td>
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<td>48</td>
<td>12%</td>
<td>49</td>
<td>13%</td>
<td>97</td>
</tr>
<tr>
<td><strong>PET4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable</td>
<td>373</td>
<td>93%</td>
<td>348</td>
<td>92%</td>
<td>721</td>
</tr>
<tr>
<td>Negative</td>
<td>347</td>
<td>93%</td>
<td>332</td>
<td>95%</td>
<td>679</td>
</tr>
<tr>
<td>Positive</td>
<td>26</td>
<td>7%</td>
<td>16</td>
<td>5%</td>
<td>42</td>
</tr>
</tbody>
</table>
AHL 2011: PFS according to the PET driven strategy

![Graph showing progression-free survival (PFS) results.]

- 2y-PFS: 95% (n = 618, 86%)
- 2y-PFS: 78% (n = 61, 8%)
- 2y-PFS: 47% (n = 42, 6%)

*according to central review*
DLBCL International Validation Study (IVS) PET2 interpretation

114 DLBCL treated with R-Chemo – aaIPI = 2-3: 65%, aaIPI = 1: 29%
FU = 39 months

3y PFS: 81% v 59%
K = 0.66 (3 observers)

3y PFS: 80% v 40%
K = 0.83 (3 observers)

E. Itti et al, EJNM 2013
R-CHOP with or without Radiotherapy in Non-Bulky Limited-Stage DLBCL: Results of the Prospective Randomized Phase III 02-03 Trial from the Lysa/Goelams Group

Radiotherapy can be avoided in PET4 negative patients without impairing outcome

T Lamy et al., ASH 2014, abstr 393
Randomized phase II
DLBCL: 18-60y
aaIPI=2-3

Induction

PET 0  PET 2  PET 4

R-ACVBP14

C1  C2  C3  C4

PET results

PET 2  PET 4+

PET-  PET+  PET2-  PET2+

consolidation

Salvage therapy

According to randomization arm

A
MTX / R-VP-IFOSFAMIDE / Arac

B
R-CHOP-14 x 4

Real time central PET review
IHP criteria

NCT00498043

Casasnovas et al, Blood 2011
LNH 2007-3B: Actual Consolidation treatment

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>Chemo</th>
<th>Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td>24%</td>
<td>26%</td>
<td>50%</td>
</tr>
<tr>
<td>2y-PFS</td>
<td>87%</td>
<td>83%</td>
<td>75%</td>
</tr>
</tbody>
</table>

RO. Casasnovas et al, ASCO 2014; Abstr 8503
LHN 2007-3B
Outcome according to ΔSUVmax PET0-2 and PET0-4

Exploratory analysis – Progression-Free Survival according to SUVmax reduction
PET0-2/ SUVmax reduction PET0-4 (ITT)
With Number of Subjects at Risk and 95% Confidence Limits

4y PFS: 86%
4y PFS: 79%
4y PFS: 35%

Exploratory analysis – Overall Survival according to SUVmax reduction PET0-2/ SUVmax reduction PET0-4 (ITT)
With Number of Subjects at Risk and 95% Confidence Limits

4y OS: 91%
4y OS: 85%
4y OS: 57%

80% of the whole population

RO. Casasnovas et al, ASCO 2014; Abstr 8503
GA In NEwly Diagnosed DLBCL - GAINED

DLBCL, 18-60y, aaIPI= 1-3: Phase III – 2 arms

CHEMO14 according to center decision:
- ACVBP14
- CHOP14

Induction

R-CHEMO14
C1 C2 C3 C4

Arm A

R

GA101-CHEMO14
C1 C2 C3 C4

Arm B

PET 0 PET 2 PET 4

PET results

△ SUV0-4 ≤ 70%

△ SUV0-4 > 70%

△ SUV 0-2 > 66%

△ SUV 0-2 ≤ 66%

consolidation

Salvage therapy

According to randomization arm and CHEMO14 regimen

R-ChOP-14 x 4
MTX / R-VP-IFOSFAMIDE / Arac

MTX / GA101-VP-IFOSFAMIDE / Arac
GA101-CHOP-14 x 4

MTX BEAM + ASCT

GA101: 1000mg by injection
D1-D8 cycles 1-2
Early treatment intensification with R-ICE and 90Y-ibritumomab tiuxetan (Zevalin)-BEAM stem cell transplantation in patients with high-risk diffuse large B-cell lymphoma patients and positive interim PET after 4 cycles of R-CHOP-14

Mark Hertberg,1 Maher K. Gandhi,2,3 Judith Trotman,4 Belinda Butcher,5 John Taper,6 Amanda Johnston,7 Devinder Gill,3 Shir-Jing Ho,8 Gavin Cull,9 Keith Fay,10 Geoff Chong,11 Andrew Grigg,12 Ian D. Lewis,13 Sam Milliken,14 William Renwick,15 Uwe Hahn,16 Robin Filshie,17 George Kannourakis,18 Anne-Marie Watson,19 Pauline Warburton,20 Andrew Wirth,21 John F. Seymour,22 Michael S. Hofman23 and Rodney J. Hicks;23 on behalf of the Australasian Leukaemia Lymphoma Group (ALLG)

PFS

OS

29% TEP4+ (IWG 2007)
Impact du volume métabolique
TMTV Assessment

- Using the Beth Israel Plug-in (*Kanoun S, PLoS One 2015*)
- A region of interest (ROI) was drawn around each foci FDG uptake.
- In each ROI, voxels presenting a threshold of 41% SUVmax were incorporated to define tumor volumes (*Meignan M, EJNM 2014*)
- Extranodal involvement:
  - the liver, lung and bone marrow were considered involved only if there was focal uptake,
  - Spleen involvement was considered if there was focal uptake or diffuse uptake >150 % of the liver background.
- All the individual tumors volume were added to compute the TMTV
AHL2011
PFS according to the TMTV

26% High TMTV

Casasnovas RO, ASCO 2016; Abs 7509
AHL 2011
PFS according to TMTV in PET2+ patients

48% of High TMTV (cut-off = 350 ml)

2y-PFS = 90.4%
2y-PFS = 60.7%

PFS by arm - Patients PET2 +
With Number of Subjects at Risk and 95% Confidence Limits

+ Censored
Logrank p=0.0129

Progression-free survival (months)

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95%CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>23</td>
<td>34.8 % (8)</td>
<td>65.2 % (15)</td>
</tr>
<tr>
<td>Low</td>
<td>25</td>
<td>8 % (2)</td>
<td>92 % (23)</td>
</tr>
</tbody>
</table>

Cut off of MTV Total : 350 cm3
TMTV impacts the outcome of DLBCL pts

114 DLBCL pts, 31% >60y, aalPI>1 = 65%, median FU = 39 months

Sassanelli et al, EJNM 2014; 41: 2017
LNH 2007-3B: Impact of TMTV on outcome

167 DLBCL
18-59y, aaIPI= 2-3

TMTV cut-off = 650 ml

PFS

OS

Median Follow up = 44.4 month

Casasnovas RO et al, ICML 2015, Abst 83
LNH 2007-3B: outcome according to TMTV and ΔSUVmax 0-4

**PFS**

<table>
<thead>
<tr>
<th>PFS (months)</th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤650 cm³ and PET0-4 SUVmax reduction ≤70%</td>
<td>108</td>
<td>13.9% (15)</td>
<td>86.1% (93)</td>
<td>NA (N)</td>
</tr>
<tr>
<td>&gt;650 cm³ and PET0-4 SUVmax reduction ≤70%</td>
<td>10</td>
<td>80% (8)</td>
<td>20% (2)</td>
<td>6.5 (1)</td>
</tr>
<tr>
<td>&gt;650 cm³ or PET0-4 SUVmax reduction &gt;70%</td>
<td>42</td>
<td>31% (13)</td>
<td>69% (23)</td>
<td>NA (N)</td>
</tr>
</tbody>
</table>

Reference is MTV ≤650 cm³ and PET0-4 SUVmax reduction >70%

**OS**

<table>
<thead>
<tr>
<th>OS (months)</th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤650 cm³ and PET0-4 SUVmax reduction &gt;70%</td>
<td>108</td>
<td>8.5% (7)</td>
<td>93.5% (101)</td>
<td>NA (N)</td>
</tr>
<tr>
<td>&gt;650 cm³ and PET0-4 SUVmax reduction ≤70%</td>
<td>10</td>
<td>4.0% (4)</td>
<td>60% (6)</td>
<td>NA (7)</td>
</tr>
<tr>
<td>&gt;650 cm³ or PET0-4 SUVmax reduction &gt;70%</td>
<td>42</td>
<td>23.8% (10)</td>
<td>70.2% (32)</td>
<td>NA (N)</td>
</tr>
</tbody>
</table>

Reference is MTV ≤650 cm³ and PET0-4 SUVmax reduction >70%

<table>
<thead>
<tr>
<th></th>
<th>4y-PFS</th>
<th>4y-OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMTV0 ≤ 650 ml and ΔSUVmax0-4&gt;70% (n = 108; 68%)</td>
<td>86%</td>
<td>93%</td>
</tr>
<tr>
<td>TMTV0 &gt; 650 ml or ΔSUVmax0-4≤70% (n = 42; 26%)</td>
<td>69%</td>
<td>72%</td>
</tr>
<tr>
<td>TMTV0 &gt; 650 ml and ΔSUVmax0-4≤70% (n = 10; 6%)</td>
<td>20%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Casasnovas RO et al, ICML 2015, Abst 83
TMTV impacts DLBCL pts prognosis through its influence on Rituximab PK

High TMTV are related to lower rituximab AUC1
($R^2 = 0.51$, $p < 0.0001$)

AUC1 < 9600 mg.h/l are associated to lower response rate, shorter PFS and OS

Casasnovas RO et al, ICML 2015, Abst 252
Tout M, RO Casasnovas et al submitted
Dose optimale de Rituximab selon le volume métabolique

\[
\text{Dose cible (mg/m}^2\text{)} = 257.59 \times (MTV_0)^{0.081}
\]

Casasnovas RO et al, ICML 2015, Abst 252
Conclusions

• La **TEP intérimaire (TEP2 / TEP4)** doit faire partie de la prise en charge des patients atteints de DLBCL et LH
  • S Legouill and O. Casasnovas, Blood 2017 (DLBCL)
  • C. Rossi and O. Casasnovas, Bull Cancer 2017 (HL)

• Les stratégies TEP guidées :
  • Nécessitent l’utilisation de **critères de positivité adaptés**
  • Nécessitent une **juste interprétation des TEP** et une bonne coopération Nucléariste/Hématologue
  • Permettent **d’optimiser le rapport efficacité / tolérance du traitement**

• **Le volume métabolique** reste encore du domaine de l’expérimentation:
  • Permet associé à la réponse précoce une meilleure stratification pronostique des patients
  • Doit démontrer son utilité pour guider le traitement ou adapter les doses d’anticorps thérapeutique (DLBCL)
Phase II study of Brentuximab Vedotin-DHAP followed by ASCT and BV maintenance in patients with baseline high total metabolic tumor volume (TMTV) Hodgkin Lymphoma (HL) and PET positive after 2 cycles of escalated BEACOPP (BEACOPPesc)

PET2

Positive

TMTV high

BV-DHAP x 2

TMTV Low

BEACOPP esc x 2

Cutoff TMTV = 350ml

PET4

Neg

ASCT

Pos

BEACOPP esc x 2

BV x 8

Salvage therapy

Improving PFS of PET2+ patients

Phase II study for PET2+ patients: increase 2y-PFS 70% -> 85%
Expected PET2+ patients accrual = 36 pts/y
Aknowledgements

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• PI H10 study
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