Diffuse large B-cell lymphomas

G. Verhoef, MD, PhD
University Hospital Leuven
BHS, March 9, 2013
Case

- A 72-year-old previously healthy man presented with acute abdominal pain and a 15 kg weight loss.
- Positron emission tomography demonstrated [18F]fluorodeoxyglucose-avid mesenteric lymphadenopathy, with evidence of bowel compression near a 3x3 cm lymph node and mediastinal lymphadenopathy.
- Bone marrow biopsy was negative, LDH normal, viral serology negative.
Diffuse Large B-cell Lymphoma

CD20

Ki67
Diffuse large B-cell lymphoma: 30% of NHL Cases

- Follicular (25%)
- Mantle cell (6%)
- Small lymphocytic (7%)
- MALT type marginal zone B cell (7.5%)
- Nodal type marginal zone B cell (< 2%)
- Lymphoplasmacytic (< 2%)
- Burkitt (2.5%)
- Other subtypes (9%)
- T and NK cell (12%)
- Diffuse large B cell (30%)

Lichtman. Williams Hematology, 7th edition. 2006;1408
DLBCL

• Classification and subtypes of DLBCL
• Prognostic factors
• Treatment guidelines
“Higby” classification for Lymphomas (NYJM, 1979)

I. Good ones
II. Not-so-good ones
III. Really bad ones
IV. Ones that are not what they seem
Aggressive B-cell lymphomas in WHO Classification 2008

<table>
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<td>Diffuse large B-cell lymphoma (DLBCL), not otherwise specified</td>
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<td>Common morphologic variants</td>
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<td>Centroblastic</td>
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<tr>
<td>Immunoblastic</td>
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<td>Anaplastic</td>
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<td>Rare morphological variants</td>
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<td>Molecular subgroups</td>
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<td>Germinal centre B-cell-like (GCB)</td>
</tr>
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<td>Activated B-cell-like (ABC)</td>
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<td>Immunohistochemical subgroups</td>
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<td>CD-5-positive DLBCL</td>
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<td>Germinal Centre B-cell like (CCB)</td>
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<td>Non-germinal centre B-cell-like (non-GCB)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma subtypes</td>
</tr>
<tr>
<td>primary DLBCL of the CNS</td>
</tr>
<tr>
<td>Primary cutaneous DLBCL, leg type</td>
</tr>
<tr>
<td>T cell/histiocyte rich large B-cell lymphoma</td>
</tr>
<tr>
<td>EBV+ DLBCL of the elderly*</td>
</tr>
</tbody>
</table>
# Aggressive B-cell lymphomas in WHO Classification 2008

## Other lymphomas of large B-cells

<table>
<thead>
<tr>
<th>Primary mediastinal (thymic) large B-cell lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular large B-cell lymphoma</td>
</tr>
<tr>
<td>DLBCL associated with chronic inflammation</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>ALK-positive large B-cell lymphoma</td>
</tr>
<tr>
<td>Plasmoblastic lymphoma</td>
</tr>
<tr>
<td>Large B-cell lymphoma arising in HHV-8-associated multicentric Castleman Disease</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
</tr>
</tbody>
</table>

## Borderline cases

<table>
<thead>
<tr>
<th>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and HL</td>
</tr>
</tbody>
</table>
DLBCL, NOS

DLBCL subtypes in specific anatomic sites

• Primary DLBCL of the central nervous system (Daan Dierickx)
  – Different clinical presentation
  – Relation between intraocular disease
  – GEP studies demonstrated some unique features
  – Link between testis DLBCL (?)
  – Different treatment and outcome

• Primary cutaneous DLBCL, leg type

• Intravascular large B-cell lymphoma
DLBCL, NOS

DLBCL subtypes in specific anatomic sites

• Primary cutaneous DLBCL, leg type
  – Often a better prognosis

• Intravascular large B-cell lymphoma
  – Rare form of DLBCL
  – Presence of large B cells only in the lumens of small vessels, particularly capillaries
  – Lymph node involvement is rare
  – Neurological symptoms
  – Often not diagnosed until autopsy
  – Most often ABC phenotype and CD5-positive
Case presentation

- 41-year old woman
- Longstanding B-symptoms
- Progressive encephalopathy
- Tachypnoe and tachycardia
- Labo: LDH↑↑↑↑
Intravascular lymphoma, stage IVE
Glomerular capillaries containing large irregular cells with infiltration of the surrounding interstitium

Courtesy department of Pathology
CD20 immunostaining of tumour cells in interstitium and glomerular capillaries
Intravascular lymphoma

- Rare subtype of extra-nodal diffuse large B-cell lymphoma
  - Characterized by proliferation of neoplastic lymphoid cells in the lumina of small vessels, particularly capillaries
- Can effect virtually every organ system
  - CNS, skin, lung, kidney, adrenals, BM
- Most frequent clinical manifestations
  - Encefalopathy
  - Cutaneous lesions
  - Fever of unknown origin
  - Interstitial lung disease, pulmonary hypertension, adrenal failure, nephrotic syndrome......
Intravascular lymphoma

- Diagnosis is often only made post-mortem
- Pathophysiology:
  - Lack of CD29 and CD54 adhesion molecules
- Prognosis:
  - Extremely aggressive
  - Because of frequent delay in diagnosis???
T-cell/histiocyte-rich large B-cell lymphoma

• Morphological variant, but with many distinctive clinical features
  – Aggressive
  – Often advanced stage
  – Splenomegaly and BM involvement
  – Relationship with nodular lymphocyte predominant Hodgkin lymphoma (NLP HL)
  – NLP HL may progress to de novo T/HRLBCL
Small number of large, atypical cells, surrounded by histiocytes and small lymphocytes.
Primary Mediastinal large B-cell lymphoma (PMBL)

Sheets of large cells with abundant pale cytoplasm
Primary Mediastinal LBCL (PMBL)

Associated interstitial fibrosis
Primary Mediastinal large B-cell lymphoma (PMBL)

- Common in adolescents and young adults
- Tumor is thought to be derived from medullary B cells within the thymus gland
- CD20 and CD79a without surface immunoglobulin
- CD30 is often positive, cREL1, TRAF1
- A GEP differing from DLBCL and resembles cHL
- Upregulation of NFκB pathway
DLBCL and MLBCL genes
Elderly patient, 65 year old

H&E  CD20  EBER in situ
EBV-positive DLBCL of the elderly

• Provisional entity, first described in elderly Japanese patients
• Patients are generally >50 years without any known immunodeficiency or prior lymphoma
• Clinical behavior is aggressive with frequent extranodal presentation
• Poor prognosis
• Sometimes overlap with classical Hodgkin with HRS-like cells
• Other variant: EBV-positive DLBCL associated with chronic inflammation
DLBCL, NOS
DLBCL, specific subtypes

**DLBCLL-UNC/BL/DLBCL**

- Distinction of BL from morphologically similar aggressive B-cell lymphoma has been problematic
- BL has characteristic GEP, but some DLBCL has similar GEP
- Most have complex karyotype often with dual translocation MYC and BCL-2
- Poor prognosis
Burkitt
CD10 +
BCL6 +
BCL2 −
Sox 11 +/−
MIB-1 > 98%
MYC simple
EBV +/−

B-UNC/BL/DLBCL
CD10 +
BCL6 +/−
BCL2 +
Sox 11 ND
MIB-1 < 90%
MYC complex
EBV −

DLBCL GCB
CD10 +
BCL6 +
BCL2 +/−
Sox 11 −
MIB-1 Variable
MYC rare +
EBV −
1. DLBCL, NOS

Courtesy T. Tousseyn
DLBCL, not otherwise specified (NOS)

- Most common
- May present in lymph node and/or extranodal
- Most common genetic aberrations:
  - *BCL6* gene (30% of cases)
  - *MYC* (up to 10%)
  - *BCL2* translocations (especially in GCB-cell subgroup)
DLBCL, not otherwise specified (NOS)

• RNA gene-expression profile
## DLBCL NOS: not one diseases

<table>
<thead>
<tr>
<th></th>
<th>Germinal B-cell like (GCB)</th>
<th>Activated B-cell like (ABC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell of origin</strong></td>
<td>Germinal center B cell</td>
<td>Post-germinal center B cell</td>
</tr>
<tr>
<td><strong>Oncogenenic</strong></td>
<td>• T (14;18) of BCL-2</td>
<td>Constitutive activation of NF-KB</td>
</tr>
<tr>
<td><strong>mechanism</strong></td>
<td>• Chr. 2p amplification of c-rel locus</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical outcome</strong></td>
<td>Favorable: 60% 5-yr survival</td>
<td>Poor: 35% 5-yr survival</td>
</tr>
</tbody>
</table>
DLBCL: variants, subgroups and subtypes

• DLBCL: not otherwise specified
• DLBCL: subtypes
  – T-cell/histiocyte-rich large-cell lymphoma
  – EBV positive DLBCL of elderly
• DLBCL: specific anatomic sites
  – Primary mediastinal
  – Intravascular
  – Leg type
  – Primary DLBCL of CNS
• Borderline cases
  – Very often including “double hit” lymphoma’s
Prognostic factors in DLBCL
“Clinical factors”
<table>
<thead>
<tr>
<th>Score</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Low risk</td>
</tr>
<tr>
<td>2</td>
<td>Low-intermediate</td>
</tr>
<tr>
<td>3</td>
<td>High-intermediate</td>
</tr>
<tr>
<td>4-5</td>
<td>High-risk</td>
</tr>
</tbody>
</table>

Staging is defined according to the Ann Arbor system. The International Prognostic Index (IPI) and age-adjusted is used for prognostic purposes.(2) Risk factors: Age >60, serum LDH>normal range, ECOG performance status≥2, Ann Arbor stage III or IV, number of extranodal sites >1
### Age adjusted International prognostic Index

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
</tr>
<tr>
<td>1</td>
<td>Low-intermediate</td>
</tr>
<tr>
<td>2</td>
<td>High-intermediate</td>
</tr>
<tr>
<td>3</td>
<td>High-risk</td>
</tr>
</tbody>
</table>

Risk factors: serum LDH>normal range, ECOG performance status≥2, Ann Arbor stage III or IV
**International Prognostic Index for non-Hodgkin lymphoma**

<table>
<thead>
<tr>
<th>International Prognostic Index(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase concentration above normal</td>
</tr>
<tr>
<td>ECOG performance status ≥2</td>
</tr>
<tr>
<td>Ann Arbor stage III or IV</td>
</tr>
<tr>
<td>Number of extranodal disease sites &gt;1</td>
</tr>
</tbody>
</table>

One point is given for each of the above characteristics present in the patient, for a total score ranging from zero to five. When applied to the initial group of 2031 patients with aggressive NHL treated with anthracycline-based regimens that did NOT include rituximab, five-year overall survival (OS) and complete response (CR) rates according to score were as follows:

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk group</th>
<th>5-yr OS, percent</th>
<th>CR rate, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>Low risk</td>
<td>73</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Low-intermediate risk</td>
<td>51</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>High-intermediate risk</td>
<td>43</td>
<td>55</td>
</tr>
<tr>
<td>4 to 5</td>
<td>High risk</td>
<td>25</td>
<td>44</td>
</tr>
</tbody>
</table>

This same score applied to 1063 patients treated with rituximab plus CHOP or CHOP-like chemotherapy predicted the following:\(^2\):

<table>
<thead>
<tr>
<th>Score</th>
<th>3-yr EFS</th>
<th>3-yr PFS</th>
<th>3-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>81</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>75</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>4 to 5</td>
<td>50</td>
<td>50</td>
<td>59</td>
</tr>
</tbody>
</table>

**Age adjusted International Prognostic Index\(^1\)**

For this score, all of the prognostic factors listed above, with the exception of age and number of extranodal sites, are given one point for a score ranging from zero to three. When applied to the group of 761 patients >60 years of age, five-year OS and CR rates according to the adjusted score were as follows:

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk Group</th>
<th>5-yr OS, percent</th>
<th>CR rate, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
<td>56</td>
<td>91</td>
</tr>
<tr>
<td>1</td>
<td>Low-intermediate risk</td>
<td>44</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>High-intermediate risk</td>
<td>37</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>High risk</td>
<td>21</td>
<td>36</td>
</tr>
</tbody>
</table>

EFS: event-free survival; PFS: progression-free survival.

Overall Survival according to IPI score

6696 patients included in GELA randomized studies

Survival Probability vs. OS (months)

IPI 0-1
IPI 2
IPI 3
IPI 4-5

Logrank p<0.0001

Courtesy A. Bosly
Case

- A 72-year-old previously healthy man presented with acute abdominal pain and a 15 kg weight loss. ECOG 1
- Positron emission tomography demonstrated [18F]fluorodeoxyglucose-avid mesenteric lymphadenopathy, with evidence of bowel compression near a 3x3 cm lymph node and lymphadenopathy upper diafragma.
- Bone marrow biopsy was negative, LDH normal, viral serology negative
- ECOG:1

Age-adjusted IPI:
1. Low
2. low-intermediate
3. High-intermediate
4. High risk

CR rate:..................
5-yr OS:...............
Case

• A 72-year-old previously healthy man presented with acute abdominal pain and a 15 kg weight loss.
• Positron emission tomography demonstrated [18F]fluorodeoxyglucose-avid mesenteric lymphadenopathy, with evidence of bowel compression near a 3x3 cm lymph node and lymphadenopathy upper diafragma.
• Bone marrow biopsy was negative, LDH normal, viral serology negative
• ECOG: 1

Age-adjusted IPI: 1 risk factor (stage)
Low-intermediate
CR rate: 71%
5-yr OS: 44%
Smith A, Br J Haematol, 2010; 148:739-753
Overall outcome in patients treated with R-CHOP

British Columbia

Outcome according to the standard International Prognostic Index (IPI).

Outcome according to the number of International Prognostic Index (IPI) factors.
Outcome according to the revised International Prognostic Index (R-IPI).

Biological prognostic factors by gene expression micro-arrays
Clinical study according to phenotype of diffuse large cells lymphomas (Alizadeh, 2000)
DLBCL: biological prognostic factors
“immuno-histology”
DLBCL: Hans algorithm
DLBCL: Hans algorithm
Case

- A 72-year-old previously healthy man presented with acute abdominal pain and a 15 kg weight loss.
- Positron emission tomography demonstrated [18F]fluorodeoxyglucose-avid mesenteric lymphadenopathy, with evidence of bowel compression near a 3x3 cm lymph node and lymphadenopathy upper diafragma.
- Bone marrow biopsy was negative, LDH normal, viral serology negative
- ECOG:1

CD10: negative
BCL-6: negative
Hans algorithm:............
OS for DLBCL patients with GCB/nonGCB DLBCL.

Survival analysis of the validation set.

A. OS by GEP
   - GCB (n=37)
   - ABC (n=26)
   \( p < 0.001 \)

B. OS by algorithm
   - GCB (n=41)
   - ABC (n=22)
   \( p < 0.001 \)

C. EFS by GEP
   - GCB (n=32)
   - ABC (n=22)
   \( p = 0.0062 \)

D. EFS by algorithm
   - GCB (n=36)
   - ABC (n=18)
   \( p = 0.012 \)
Kaplan-Meier survival curves of event-free survival (EFS) of 62 DLBCL cases stratified according to the IHC algorithm of: A, Choi et al.

Prognosis and “Double-hit” lymphoma

• Term is used colloquially to refer to cases of lymphoma that contain translocations of both c-MYC gen at 8q24 and a second site, often BCL-2 gene at 18q21 (or BCL-6 gene)

• Most cases would be best considered “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (WHO 2008)

• Translocations involving c-MYC: 5-15 % of cases of DLBCL and confer a worse prognosis after CHOP treatment

• Translocations only involving BCL-2 gene are seen in ± 30% of DLBCL cases and do not appear to impact survival

• However, BCL-2 translocated germinal center subtype DLBCL is associated with inferior outcome

• Combination between translocation c-MYC and translocation BCL-2 (± 5%): worse prognosis (median survival 6-18 months)
Overall survival and progression-free survival of patients with DLBCL according to (A) the presence of BCL2 translocations alone or concomitant MYC breaks stratified by GEP-defined subgroups; (B) BCL2 translocations stratified with GEP subgroups in the vali...
“Double-hit” and “double expression” lymphoma

• c-MYC translocation=increased c-MYC expression
• Overexpression of c-MYC without c-MYC translocation has also been described and is due to amplification
• Overexpression of c-MYC and overexpression of BCL-2 can be identified by immunohistochemistry and is seen in 21-29% of patients
• Patients with double expression, but without the rearrangement have also a lower CR rate and shorter overall survival
Overall (OS) and progression-free survival (PFS) of patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone according to presence of concurrent expression of MYC and BCL2 proteins (M...
Case

• A 72-year-old previously healthy man presented with acute abdominal pain and a 15 kg weight loss.
• Positron emission tomography demonstrated [18F]fluorodeoxyglucose-avid mesenteric lymphadenopathy, with evidence of bowel compression near a 3x3 cm lymph node and lymphadenopathy upper diafragma.
• Bone marrow biopsy was negative, LDH normal, viral serology negative
• No rearrangements of MYC en BCL2, EBER in situ negative

CMYC+ (>40%)  BCL2+ (>50%)
Staging workup

- Patient history, physical examination
- Performance status, B-symptoms
- Complete blood count, chemistry including LDH
- Screening for hepatitis B, C, HIV
- Electrophoresis
- Lymph node biopsy (fine-needle aspirate is inadequate)
- PET-CT scan
- Bone marrow aspirate/biopsy (if negative PET-CT)
- MRI for suspected CNS localisation
- Spinal tap in patients with:
  - Paranasal sinus, testicular, epidural, breast, bone marrow, presence of two or more extranodal sites, HIV
Role of PET(CT) scan in DLBCL

• Initial staging ✓
  – Leads to a change in stage in up to 20-40%
  – This changes the treatment choice in 5-15%

• Interim PET for response assessment ✓

• Interim PET to direct treatment ?

• Restaging at completion of therapy ✓

• Screening for relapse: no
Tussentijdse opvolging van chemotherapie
## Early treatment evaluation with PET

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Pet after...</th>
<th>2-year outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerusalem (2000)</td>
<td>28</td>
<td>3 cycles</td>
<td>PET- 62% PFS</td>
</tr>
<tr>
<td>Spaepen (2002)</td>
<td>70</td>
<td>3 cycles</td>
<td>PET+ 0% PFS</td>
</tr>
<tr>
<td>Kostakoglu (2002)</td>
<td>30</td>
<td>1 cycle</td>
<td>PET- 85% PFS</td>
</tr>
<tr>
<td>Haioun (2005)</td>
<td>90</td>
<td>2 cycles</td>
<td>PET+ &lt;15% PFS</td>
</tr>
<tr>
<td>Michael (2005)</td>
<td>121</td>
<td>2 cycles</td>
<td>PET- 87% PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PET+ 34% PFS</td>
</tr>
</tbody>
</table>
The use of interim PET to direct therapy

• If negative, continue treatment
• High negative predictive value
• Positive predictive value: 20-80%
  – Inflammation, blood glucose level, tumor size, time from last treatment etc, interpretation of + versus –
• If positive, ????? Study!
• Clinicians need:
  – Simple positive or negative criteria
  – Easy to interpret
  – High positive and negative value
Visual assessment of PET

- IHP: comparison between baseline mediastinal blood pool activity and lymph nodes sites of involvement
- Deauville score: negative 1-3, positive 4 or 5
  - Score 1: no uptake
  - Score 2 uptake: ≤mediastinum
  - Score 3 uptake: >mediastinum but ≤liver
  - Score 4 uptake: >liver and new sites of disease
  - Score X: new areas of uptake unlikely to be related to lymphoma
Semiquantitative method: $\Delta SUV_{\text{max}}$

- **Baseline PET (PET0):**
  - SUV max in the most active lesion
- **Interim PET:**
  - If (+): SUV max in the most active lesion
  - If (-): SUV max in the area of PET0
- **Calculation of % of SUV max reduction**
- **Optimal cut-off determined by ROC**
  - 66% for $\Delta SUV_{\text{maxPET0-2}}$
  - 72.9% for $\Delta SUV_{\text{maxPET0-4}}$
Positive interim PET: Biopsy-proven method

- MSKCC: all patients with positive I-PET underwent biopsy
- Therapy was only changed in patients with biopsy-proven lymphoma
- >80% of all biopsies were false-positive!!!
Role of PET(CT) scan in DLBCL

• Restaging at completion of therapy  
  – Standard of care  
  – PET-: highly predictive of progression-free and overall survival  
  – PET+: consolidation with radiotherapy ?

• Screening for relapse: no  
  – Imaging-detected relapse is not associated with improved survival  
  – Very high number of false-positive results (80% of patients will have unnecessary biopsies!)  
  – Increased radiation exposure (risk of malignancies, especially in younger patients?)  
  – Expensive!
Survival of patients with DLBCL

Belgian guidelines newly diagnosed DLBCL

G. Verhoef, W. Schroyens, D. Bron, C. Bonnet, V. De Wilde, A. Van Hoof, A. Janssens, D. Dierickx, M. André, E. Van Den Neste

Based on 2011 ESMO and NCCN version 4.2011 and amended for the particular Belgian context
Limited stage

- Good riks patients (age-adjusted IPI 0, 1, non-bulky, no B-symptoms:

  - R-CHOP 21 days x 6
    or
  - R-CHOP x 3 and involved field radiation
Limited stage

- Young patients (<61 years) IPI low risk with burk or IPI low-intermediate:
- R-CHOP 21 days x 6 + IFR on bulk

- Young patients (age 18-59) with IPI 1:
- R-ACVBP x 4 and consolidation
Advanced stage (age-adjusted IPI≥2, bulky>10cm, stage IIIB, III-IV

• “Fit” advanced:
  – 8x R-CHOP-21 or 6x R-CHOP-14 + 2R
  – Autologous transplantation after consolidation in selected patients or slow-responders: clinical trial

• Advanced older patients “unfit” for R-CHOP
  – Geriatric assessment
  – Supportive care (anti-infectious, growth factors)
  – Consider R-miniCHOPx6
  – Pre-phase with steroids +/- vincristine
CNS prophylaxis

• No consensus
• Paranasal sinus, testis, bone marrow and ≥ one extranodal sites: 4 doses of intrathecal MTX and/or arac
• LySA: IPI ≥1: 4 injections of MTX