Lymphoma- Med A-new drugs and treatments

Silvia Montoto

Lisbon, 19/03/2018
Disclosures: Roche, Gilead

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Lisbon, 19/03/2018
Outline

• Lymphoma- what is it?
  - Classification
  - Why does it matter

• Most frequent types of lymphoma
  - DLBCL
  - FL
  - HL

• Treatments

• New drugs
  - PI3K inhibitors
  - Bruton tyrosine kinase inhibitors (BTKi)
  - Checkpoint inhibitors
  - BCL-2 antagonists
  - New monoclonal antibodies (MoAb)
Definition of lymphoma

HETEROGENOUS group of malignant neoplasms arising in the reticuloendothelial and lymphoid system.

- Hodgkin lymphoma
- Non-Hodgkin lymphomas
Classification of lymphomas

• Non-Hodgkin lymphomas
  - B-cell lymphomas
  - T-cell lymphomas

• Hodgkin lymphoma
Clinico-pathological entities defined by

- Morphology
- Immunology
- Genetics
- Molecular
- Clinical
### Classification of lymphoma and MED-A

From WHO 2008!!

<table>
<thead>
<tr>
<th>B-Cell Neoplasms</th>
<th>International Prognostic Scoring System for Waldenstrom's Macroglobulinemia (IHW-PM)</th>
<th>International Prognostic Index (IP)</th>
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<tbody>
<tr>
<td>Cafeine marginal zone lymphoma</td>
<td>Low risk (1-3 score points except age 65+)</td>
<td>Low risk</td>
</tr>
<tr>
<td>Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT)</td>
<td>Intermediate risk (score 2 or age 65 alone)</td>
<td>Intermediate-risk (I-R)</td>
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<tr>
<td>Neoplastic marginal zone lymphoma</td>
<td>High risk (3+)</td>
<td>ECOG (Eastern Cooperative Oncology Group)</td>
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<tr>
<td>Lymphoplasmacytic lymphoma (LPL)</td>
<td>Not evaluated</td>
<td>NOT evaluated</td>
</tr>
</tbody>
</table>

| Diffuse large B-cell lymphoma (DLBCL, NOE) | Primary DLBCL, not the NHL | NOT evaluated |
| T-cell/hodgkin rich large B-cell lymphoma | Primary DLBCL, not the NHL | NOT evaluated |
| MALT associated with chronic inflammation | Lymphomatoid granulomatosis | Primary mediastinal (thymus –) large B-cell lymphoma |
| MALT associated with chronic inflammation | Intravascular large B-cell lymphoma | NOT evaluated |
| Large B-cell lymphoma, unclassified, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (intermediate CL/BM/BK) | Large B-cell lymphoma, unclassified, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (intermediate CL/BM/BK) | NOT evaluated |
| Burkitt lymphoma (BL) | Burkitt lymphoma (BL) | NOT evaluated |
| Other T-cell, specific | Other T-cell, specific | NOT evaluated |
| Transformed from another type of lymphoma | Transformed from another type of lymphoma | NOT evaluated |
| No | Yes | NOT evaluated |

<table>
<thead>
<tr>
<th>Date of original diagnosis</th>
<th>Indicates the type of the original lymphoma</th>
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<tbody>
<tr>
<td>Indicates the type of the original lymphoma</td>
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</table>
### Classification of lymphoma and MED-A

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<tr>
<th>Abnormality</th>
<th>Absent</th>
<th>Present</th>
<th>FISH used</th>
<th>Not Evaluated</th>
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<tbody>
<tr>
<td><strong>Mantle cell lymphoma or Waldenstrom macroglobulinaemia</strong></td>
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<tr>
<td><strong>BL or &quot;Intermediate DLCBL/Burkitt Lymphoma&quot;</strong></td>
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<td>t(2;8)</td>
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<tr>
<td>t(8;14)</td>
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<td>t(8;22)</td>
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<tr>
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<tr>
<td>myc rearrangement</td>
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<td>X</td>
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<tr>
<td>BCL-2 rearrangement</td>
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<tr>
<td>BCL-6 rearrangement</td>
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</tbody>
</table>

High-grade lymphoma with *MYC* and *BCL-2* rearrangement
### WHO 2016-Lymphoma classification B-

<table>
<thead>
<tr>
<th>Mature B-cell neoplasms</th>
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<tbody>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
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<tr>
<td>Monoclonal B-cell lymphocytosis*</td>
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<tr>
<td>B-cell prolymphocytic leukemia</td>
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<tr>
<td>Splenic marginal zone lymphoma</td>
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<tr>
<td>Hairy cell leukemia</td>
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<tr>
<td>Splenic B-cell lymphoma/leukemia, unclassifiable</td>
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<tr>
<td>Splenic diffuse red pulp small B-cell lymphoma</td>
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<tr>
<td>Hairy cell leukemia-variant</td>
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<tr>
<td>Lymphomas asocitic lymphoma</td>
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<tr>
<td>Waldenstrom macroglobulinemia</td>
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<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS), IgM*</td>
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<tr>
<td>( \mu ) heavy-chain disease</td>
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<td>( \gamma ) heavy-chain disease</td>
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<tr>
<td>( \alpha ) heavy-chain disease</td>
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<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*</td>
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<tr>
<td>Plasma cell myeloma</td>
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<tr>
<td>Solitary plasmacytoma of bone</td>
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<tr>
<td>Extramedullary plasmacytoma</td>
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<tr>
<td>Monoclonal Immunoglobulin deposition diseases*</td>
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<tr>
<td>Extramedullary marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)</td>
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<tr>
<td>Nodal marginal zone lymphoma</td>
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<tr>
<td>Pediatric nodal marginal zone lymphoma</td>
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<tr>
<td>Follicular lymphoma</td>
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<tr>
<td>In situ follicular neoplasia*</td>
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<tr>
<td>Duodenal-type follicular lymphoma*</td>
</tr>
<tr>
<td>Pediatric-type follicular lymphoma*</td>
</tr>
<tr>
<td>Large B-cell lymphoma with IRF4 rearrangement*</td>
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<tr>
<td>Primary cutaneous follicle center lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>In situ mantle cell neoplasia*</td>
</tr>
</tbody>
</table>

### Diffuse large B-cell lymphoma (DLBCL), NOS
- Germinal center B-cell type* 
- Activated B-cell type* 
- T-cell/histiocyte-rich large B-cell lymphoma 
- Primary DLBCL of the central nervous system (CNS) 
- Primary cutaneous DLBCL, leg type 
- EBV⁺ DLBCL, NOS* 
- EBV⁺ mucocutaneous ulcer* 
- DLBCL associated with chronic inflammation 
- Lymphomatoid granulomatosis 
- Primary mediastinal (thymic) large B-cell lymphoma 
- Intravascular large B-cell lymphoma 
- ALK⁺ large B-cell lymphoma 
- Plasmablastic lymphoma 
- Primary effusion lymphoma 
- HHV8⁺ DLBCL, NOS* 
- Burkitt lymphoma 
- Burkitt-like lymphoma with 11q aberration* 

**High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangement**

**High-grade B-cell lymphoma, NOS**

- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
### WHO 2016-Lymphoma classification T-NHL and HL

#### Mature T and NK neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK-cell leukemia
- Systemic EBV+ T-cell lymphoma of childhood
- Hydrosa vacciniforme-like lymphoproliferative disorder
- Acute T-cell leukemia/lymphoma
- Extramedullary NK/T-cell lymphoma, nasal type
- Sarcomatoid-associated T-cell lymphoma

#### Monomorphic epithelioid intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome

#### Primary cutaneous CD30+ T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma

#### Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8+ T-cell lymphoma
d- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma
- Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder

#### Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TFH phenotype

### Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

### Posttransplant lymphoproliferative disorders (PTLD)
- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis PTLD
- Florid follicular hyperplasia PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma PTLD

### Histiocytic and dendritic cell neoplasms
- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease
Overall survival in patients with NHL

NHL Classification Project, 1997
Impact of molecular abnormalities on outcome

Herrera et al, J Clin Oncol, 2017
Non Hodgkin lymphoma

- Median age at diagnosis: 65 yrs
- >13,000 new cases/year in UK
Frequency of subtypes of NHL

DLBCL 36%

FL 24%

Other subtypes:
- 6%
- 2%
- 8%
- 1%
- 2%
- 7%
- 7%
- 7%

NHL Classification Project, 1997
Diffuse large B cell lymphoma: clinical characteristics

- Median age: 60-70 years
- Advanced stage: 50-60%
- BM involvement: 15-20%
- Primary extranodal: 20-30%
How bad is DLBCL?

ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA, A POTENTIALLY CURABLE DISEASE

RESULTS WITH COMBINATION CHEMOTHERAPY

Vincent T. DeVita, Jr.  George P. Canellos
Bruce Chabner  Philip Schein *
Susan P. Hubbard  Robert C. Young

Medicine Branch, National Cancer Institute,
National Institutes of Health, Bethesda,
Maryland 20014, U.S.A.

Lancet, February 1, 1975
Treatment of DLBCL

The PARMA trial for relapsed/resistant DLBCL: chemotherapy vs HDT-ASCR

5-yr EFS: 46% vs 12%  \( P = 0.001 \)

5-yr OS: 53% vs 32%  \( P = 0.038 \)

Lymphoma Registry: SCT for DLBCL 1997-2016

Number of SCTs:

- AutoSCT
- AlloSCT

Years:
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
Follicular lymphoma: clinical characteristics

- Median age: 50-60 yrs
- Good performance status
- Advanced stage: 80%
- BM infiltration: 60%
Follicular lymphoma

- Long survival
- Multiple relapses
- Risk of histological transformation
- Incurable (with conventional treatment)

Barts 1997-2007
## FL: treatment options

<table>
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<tr>
<th></th>
<th>Morbidity</th>
<th>Mortality</th>
<th>Symptomatic improvement</th>
<th>Response rate</th>
<th>Prolonged response</th>
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<tr>
<td>Rituximab</td>
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<td>Radio-MoAb</td>
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<td>+</td>
<td>+++</td>
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<tr>
<td>Rituximab + PQT</td>
<td>++</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>AutoSCT</td>
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<td>AlloSCT</td>
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</tbody>
</table>
Hodgkin lymphoma

- 1500 new cases every year in the UK
- Incidence: 3/100,000/year

- Bimodal age distribution: 15-34 yrs, > 60 yrs

- Male/female ratio: 1.4:1
Survival of adult patients with HL
Is there a 2\textsuperscript{nd} chance?

Schmitz et al, Lancet, 2002
Lymphoma Registry: SCT for HL 1997-2016

Number of SCTs

- **AutoSCT**
- **AlloSCT**
Treatment options for patients with lymphoma

- Radiotherapy
- Single agent chemotherapy
- Combination chemotherapy
- Stem cell transplant (autologous, allogeneic -sibling, MUD, RIC-)
- Immunotherapy (monoclonal antibodies, CAR-T cells...)
- Pathway inhibitors (targeted agents)
Pathways inhibitors
Families of new drugs

• PI3K inhibitors:
  - Idelalisib
  - Copanlisib

• Bruton tyrosine kinase inhibitors:
  - Ibrutinib
  - Acalabrutinib

• Checkpoint inhibitors:
  - Nivolumab
  - Pembrolizumab

• BCL-2 antagonists:
  - Venetoclax

• New monoclonal antibodies (MoAb)
  - Brentuximab vedotin
  - Obinutuzimab

MCL, CLL, DLBCL
FL
HL
FL
New monoclonal antibodies

Murine:
tositumOmab (B1)
ibritumOmab tiuxetan

Chimeric: rituxImab

Humanised:
veltuZUmab (2nd generation)
obinutuZUmab: GA101 (3rd generation)

Human: ofatumUmab (2nd generation)
Types of monoclonal antibodies
Idelalisib in R/R iNHL

RR 57%, CR: 6%

Checkpoint inhibitors + rituximab in 29 rFL

RR 66%, CR: 52%

Westin R et al, Lancet Oncol, 2014
Brentuximab vedotin post HDT-ASCR

Moskowitz CK et al, Lancet, 2015
New drugs and SCT

• Use of new drugs
  - As bridge to SCT
  - Relapse post SCT
  - Maintenance post SCT

• Concerns
  - Efficacy of SCT after new drugs
  - Toxicity of SCT after new drugs
  - (Diminish the role of SCT)
LWP studies involving new drugs

- 2013-N-02i Pwi prior to SCT
- 2013-N-02, 2016-R-01 PWI pre and post allo studies
- 2015-R-01A BV as bridge to SCT in ALCL
- 2015-R-01H BV as bridge to SCT in HL
- 2015-R-01H BV post allo in HL
- 2016-S-01 Checkpoint inhibitors pre/post alloHCT
- 2017-R-05 Ibru post ASCT MCL
# MED-A and new drugs

<table>
<thead>
<tr>
<th>Treatment pre-HSCT</th>
<th>Enter first day of treatment and mark all drugs from that date until conditioning</th>
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<tbody>
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<tr>
<td>Yes</td>
<td>Date of treatment: ----------- yyy-mm-dd</td>
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</tbody>
</table>

**Drugs given**

**Antibodies:**
- □ Alemtuzumab (MabCampath) (CD52)
- □ Brentuximab (Adcetris) (CD30)
- □ Obinutuzumab (Gyzeva) (CD20)
- □ Ofatumumab (Azerra) (CD20)
- □ RituXimab (Mabthera) (CD20)
- □ other antibody, specify________

**Radioimmunotherapy:**
- □ Bexar (CD20) (radiolabelled MoAB)
- □ Zevalin (CD20) (radiolabelled MoAB)

**Specific inhibitors:**
- □ ABI-199 (BCL2 Inhibitor)
- □ Crizotinib (ALK-Inhibitor)
- □ CC-292 (B cell receptor kinase inhibitor)
- □ Ibrutinib (B cell receptor kinase inhibitor)
- □ Idelalisib (B cell receptor kinase inhibitor)
- □ other inhibitor, specify________

**Other:**
- □ Bortezomib (Velcade)
- □ Lenalidomide (Revlimid)
- □ Other, specify __________________________

**Relapse/progression under this drug**

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<th>No</th>
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Conclusions

• New insights into the biology of lymphoma
  - New entities
  - Sub-types with worse prognosis
  - New drugs

• Main focus of research: relationship between new drugs and SCT
Thank you!

@LymphomaWP_EBMT