High-grade B-cell lymphoma: What does the clinical oncologist need from the pathologist, and why?

URBAN NOVAK, MD
Department of Medical Oncology
• No conflicts of interest to declare

...but an interest in the conflicts related to this topic!
High-grade B-cell lymphoma – the clinicians view

Is a new classification needed?

World Health Organization Classification of Tumours

Pathology & Genetics
Tumours of Haematopoietic and Lymphoid Tissues

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

"it is as sure as death & taxes that there will be a new lymphoma classification"

2001  2008

Courtesy: S. Dirnhofer (adapted)
A PRACTICAL CLASSIFICATION OF LYMPHOMAS

To the Editor: It is becoming more difficult to understand pathologists when they talk about the malignant lymphomas. Therefore, I have devised a practical classification designed to supersede the systems now commonly used. It has the advantage of being precise, predictive and relatively simple to apply.

I. Good ones (includes nonconvoluted diffuse centrilobulated histioblastoma, immune binucleolar hyperbolic folliculated macrolymphosarcoma, T1-terminal transferase-negative bimodal prolymphoblastic leukosarcoma, Jürgen-Kreuzart-Munier-Abdullah syndrome and reticulated histioblastic pseudo-Szézre IgM-secreting folliculoma).

**Characteristics:** Small tumor that does not recur after treatment.

II. Not-so-good ones (formerly “hairy-cell” pseudoincestuoblastoma, quasiconvoluted binucleate germinoma, sarcoblastiocytoma, Syrian variant of heavy-chain disease and German grossobecinioma).

**Characteristics:** Such tumors disappear on treatment but return and cause appreciable mortality.

III. Really bad ones (include farciial mononuclear diffuse convoluted pseudoquasihistiolymphosarcomyeloblastoma, IgG variant of fragmented plasmatic gammopathy, triconvolutied ipsilateral rhomboid fever, Armour’s hyperthermic caninoma and Hohner’s harmonica).

**Characteristics:** Regardless of treatment, such tumors keep growing.

IV. Ones that are not what they seem (include gallbladder disease, appendicitis, shotgun wounds and ingrown toenails).

**Characteristics:** These conditions are not actually lymphomas but are included for the sake of completeness.

Buffalo, NY 14263

DONALD J. HIGBY, M.D.
Roswell Park Memorial Institute

Higby DJ, NEJM 1979
What does the clinical oncologist need from the pathologist, and why?

...a lymphoma classification & diagnosis considering the advances...

- in molecular biology,
- clinical epidemiology,
- and incorporating smart observations by experienced hematopathologists

...and why?
High grade B-cell lymphoma (HGBCL)…

…a new category replacing BCL-u (iBL/DLBCL)

Courtesy: S. Dirnhofer
R-CHOP21 IS (STILL) THE STANDARD

- 6 x R-CHOP or 3-4 x R-CHOP ⇒ IFRT

reasonable option for stage IA or IIA non-bulky DLBCL

Persky, JCO 2008; Stephens JCO 2016

- R-CHOP for advanced DLBCL
GOING BEYOND R-CHOP$_{21}$…

• Shorter treatment intervals ?  
  no advantage (french & british)

• Maintenance rituximab ?  
  no advantage, men ?

• Continuous infusions ?

• Radiotherapy to bulks ?

• Front-line autotransplants (young, fit) ?

• CNS prophylaxis ?  
  no randomized evidence

• Specific regimens for some primary sites ?

• PET response-adapted treatments ?

• Addition of another drug (chemo) ?
Adding Etoposide to (R-)CHOP?

NHL-B2

<table>
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<td>CHOP-14 vs CHOP-21</td>
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<td>0.63;1.07</td>
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<td>0.77</td>
<td>0.59;1.02</td>
<td>.064</td>
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<td>LDH greater than normal</td>
<td>1.75</td>
<td>1.40;2.17</td>
<td>&lt; .001</td>
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<td>Stage III/IV</td>
<td>1.94</td>
<td>1.56;2.42</td>
<td>&lt; .001</td>
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<td>Bulky disease</td>
<td>1.10</td>
<td>0.90;1.36</td>
<td>.353</td>
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NHL-B1

young, good prognosis (IPI < 2, normal LDH)

Elderly  no benefit & toxic
Younger  tested in good-risk!; with Rituximab: benefit no longer present

→ R-CHOP vs. R-CHO(E)P with equal PFS (Schmitz & Vitolo, ASH 2013)
HIGH-DOSAGE CONSOLIDATION OF CR / PR PATIENTS

Phase III

GOELAMS 075  R-CHOP-14 x 8 vs. R-HDT: Equal ORP (ASCO’11)

DLCL04 FIL  R-(Mega)CHOP14 ± HDC: 2y PFS 71 vs. 59 %, equal OS (11-ICML)

Cave

Combined endpoint: PFS & OS

Not powered for a difference R-CHOP → HDT vs. R-CHOP (just consolidation)

IPI 4 & 5 only

Stiff, NEJM 2013
High-grade B-cell lymphoma – the clinicians view

A disappointment for many: the CALGB/Alliance study 50303

1st line treatment of 465 non-selected DLBCLs

Yet, no subtype information communicated

Wilson, ASH 2016;abstract 469
THERE IS A BETTER CHEMOTHERAPY THAN R-CHOP!

Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial

Good risk patients (aaIPI1, < 60 years

8 x R-CHOP$_{21}$ vs. 4 x R-ACVBP

Profit for ABC, Molina JCO 2014
Clinicians tend to mix it up: prognostic and predictive factors

Prognostic biomarker

→ Information on outcome/natural history of disease, regardless of therapy

Predictive biomarker

→ Information about the response to a given therapy

→ Some factors are both prognostic and predictive

Mary Cianfrocca, Lori J. Goldstein
The Oncologist 2004; 9: 606-616
High-grade B-cell lymphoma – the clinicians view

Example of a teacher: \( \rightarrow \text{breast cancer!} \)

- Basal
- Luminal A
- Luminal B
- HER2/neu

<table>
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<th>Basal</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2/neu</th>
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<td>ER-Negative</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
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<td>ER-Positive</td>
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<tr>
<td>ER-Positive or ER-Negative</td>
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</tr>
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</table>

- ER / PR
- HER2/neu
- Proliferation

ER & HER2: predictive impact

**ER +**

Benefit from **Tamoxifen**

**ER -**

Ø

**Trastuzumab**

Stunning –50% risk of relapse! HER2+ no longer prognostic!

Hayes, BCRT 1998; EBCTCG Lancet 2011
Romond, NEJM 2005; Piccart NEJM 2005
DLBCL: tailored treatment of its heterogeneity

- Risk-adapted therapy
  
  → Higher aaIPI score ?

  → Bulky disease ?

- Therapy based on molecular features ?

  «a nasty disease needs more therapy…!»

  → Many prognostic (bio)markers, few if any predictive (bio)marker

  → would you give Rituximab to a patient with a CD20- PMBL ?
What does the clinical oncologist need from the pathologist, and why?

...a lymphoma classification & diagnosis driven by

• predictive rather than prognostic biomarkers!

The field (incl. clinicians) should embrace the idea that:

• Targeted therapy with a target simply works better

...and why?

• Targeting the whole population is not (cost) efficient

→ Can we be satisfied with a RR of ~30 % with a targeted drug?
NEW WHO CLASSIFICATION: MOST IMPORTANT CHANGES

• **NEW**
  - High grade B-cell lymphomas NOS ≠ BCLUS
  - High grade B-cell lymphomas with MYC/BCL2/BCL6

• **Subtype required**
  - GCB vs. ABC

• **Prognostic factors**
  - Myc, Bcl2
  - MYC/BCL2/BCL6
THE COO SUBTYPES OF DLBCL

```
Hans, Blood 2004

Not standardized in CH!
Reber, Swiss Medical Weekly 2013
```

```
CD10
- BCL6
  + MUM1
    - Non-GC
      + Non-GC
      - GCB
```

```
MBL
GCB
DLBCL
ABC
DLBCL
```

```
ABC
DLBCL
GCB
DLBCL
PMBL
```

**IHC algorithms will never be reproducible**
R. Gascoyne

**Not standardize in CH!**
Be aware: the lymphoma field might also have to deal with «tests»

These patients do not need chemotherapy!

*However: Ki-67 (= standard) not in the manuscript!*

Mammaprint® not better than current practice!

*Cardoso NEJM 2016*
High-grade B-cell lymphoma – the clinicians view

COO SUBTYPES ARE FAR MORE COMPLEX…

GCB-DLBCL
- BCL2 translocation
- CMYC translocation
- EZH2 mutations
- BCL6 prom. mutations
- MEF2B mutations
- GNA mutations

Mutations: MLL2/MLL3, CREBBP/EP300
Loss: B2M & CD58
BCL6 translocations

ABC-DLBCL
- A20 loss
- CARD11 mutations
- CD79A/B mutations
- MYD88 mutations
- BLIMP1 loss
- BCL2 amplification

PMBL
- 9p24 amplification
- CIITA translocation
- STAT6 mutations
- JAK2 mutations
- REL amplification
- SOCS1 mutations

NF-κB activation

NF-κB: SURROGATE FOR A THERAPEUTIC TARGET !?!

**canonical**

**alternative**

- survival, proliferation & differentiation

**NF-κB pathways**

60 % ABC, 30 % GCB

Compagno, Nature 2009

Immunohistochemistry?
DLBCL COO SUBTYPES: NO LONGER PROGNOSTIC…

…and not yet predictive!!

**PROGNOSTIC?**

- PFS (2y) ABC 40 % (Lenz, NEJM 2008)
- non-GC 62 % (Fu, JCO 2008)
- PYRAMID (R-CHOP ± Bortezomib, ASH’15 # 811)
  - R-CHOP performed better (2y PFS 78%)
  - Selected population in randomized trials?

**PREDICTIVE?**

Randomized evidence: add bortezomib, a purported NF-κB inhibitor, to R-CHOP:

→ outcome of the NF-κB dependent ABC / non-GC subtype not improved!

Offner Blood 2015, Leonard ASH’15 # 811, Davies ASH’15 # 812

Likewise: post-hoc analysis of RICOVER

( Ott, Blood 2010)
What does the clinical oncologist need from the pathologist, and why?

...a lymphoma classification & diagnosis driven by

• Reproducible (robust & standardized) protocols

...and why?

If deemed crucial, (some impatient) clinicians do not mind if some of your valuable work is replaced by a “test”
High-grade B-cell lymphoma – the clinicians view

Outcome of DLBCLs treated with R-CHOP,

Double expressors (DEL)  Double hit (DH)

Johnson, JCO 2012  Green, JCO 2012

...VERIFICATION IN A PROSPECTIVE TRIAL!
HIGH-GRADe B-CELL LYMPHOMA – THE CLINICIANS VIEW

DIAGNOSTIC APPROACH TO HBCL: DOES GENETICS REALLY TRUMP MORPHOLOGY

ALL-like R-CHOP+ ? R-CHOP+ ? R-CHOP

Study
High-grade B-cell lymphoma – the clinicians view

HOVON-127 trial for BL to be launched soon…

Newly diagnosed high risk Burkitt Lymphoma

Arm A

1 cycle of R-CODOX-M

1 cycle of R-IVAC

(PET-) CT scan

PD

SD, PR, CR

1 cycle of R-CODOX-M

1 cycle of R-IVAC

Off protocol treatment

Arm B

q 3 weeks

3 cycles of DA-EPOCH-R

(PET-) CT scan

PD

SD, PR, CR

q 3 weeks

3 cycles of DA-EPOCH-R

Off protocol treatment

Dunleavy, NEJM 2013

Zürich, Mai 13, 2017 - Urban Novak
As a clinician,…
…I need predictive markers to guide my therapy
…I don’t mind prognostic markers once I have a proven better therapy than R-CHOP

DLBCL treatment is **NOT** keeping up with progress in molec. pathology/biology

I accept that one needs to split before you can lump again (**N.L. Harris**)

Hematoncologists should…
…not ignore their gut feelings, but should not believe that this is enough
…listen, talk, and continuously discuss with **pathologists before**…
High-grade B-cell lymphoma – the clinicians view
DA-EPOCH-R – TOO GOOD TO BE TRUE?

BURKITT’S LYMPHOMA

Event-Free Survival

Median follow-up: 5 years

Overall Survival

Median follow-up: 5 years

MYC+ DLBCL

EFS
83 % (MYC+) vs. 76 % (MYC-)

P=0.59

Median follow-up 48 months

Prospective multi-center validations ongoing

Dunleavy, NEJM 2013

Dunleavy, 11-ICML #71

Blood 2009
Principles in the (future) treatment of DLBCL

- Relapse/progression within 1 y → poor  
  Mareschal, Genes Chromosomes & Cancer 2016

- EFS > 12 months → excellent  
  Maurer JCO 2014

1. Hit early and hard („one shot disease“)
2. Develop new concepts beyond chemotherapy
3. Achieve / restore immunological control

Current

Induction → R-CHOP (like) → HDT + ASCT ?? → Maintenance

Future

Induction → R-CHOP (like) → CAR T-cells (for immunological control) → Consolidation

Neelapu, ASH 2016; LBA-6
High-grade B-cell lymphoma – the clinicians view

- aIPI < 2
  - Young, low risk
  - Elderly

- aIPI ≥ 2
  - Young, high risk
  - Elderly

≤ 60 Years

RICOVER-60: 6 x R-CHOP-14 + 2 x R
Gela LNH 98-5: 8 x R-CHOP-21

> 60 Years

Courtesy by C. Renner
THE ACHILLES’ HEEL OF ABC-DLBCL
OFFERS MULTIPLE THERAPEUTIC TARGETS

High-grade B-cell lymphoma – the clinicians view

- SYK
- BTK
- PI3K
- AKT
- mTOR

- ENZASTAURIN
- CD79A,B
- CD40 Ligand
- CD40 Receptor

- FOSTAMATINIB
- IBRUTINIB
- IDELALISIB
- EVEROLIMUS

- BORTEZOMIB
- LENALIDOMIDE

THE DNA damage response
Differentiation
Cell cycle arrest

Centrocyt
High-grade B-cell lymphoma – the clinicians view

...+ LENALIDOMIDE (R²-CHOP)

Small numbers!
Vitolo, Lancet Oncol 2014

...& IBRUTINIB (R-CHOP „Brut“)

Compared to historical controls
Nowakowski, JCO 2015

→ Problematic: the phase III (ROBUST, also in CH) will include ABC-DLCL only

Phase Ib with R-CHOP & Ibrutinib: « well tolerated & could improve responses »
Phase III ongoing
Younes, Lancet Oncol 2014
„EXPRESSOR“ VS. „HIT“ LYMPHOMA
THE MYC PROTEIN

• Expressed in 30 % of DLBCLs (vs. MYC translocation in 10 % only)

• Positive = expressed in 40 % of tumor cells

• Screening tool for translocation
  • expressed in 40-70 % of cells → 33 % will have a MYC translocation

• Negative prognostic impact only in double expressors (DEL) Myc+/Bcl2+
  • more common in the ABC subtype

• Prognosis: Myc-/Bcl2- > Myc+/Bcl2+ > DH/TH DLBCLs  
  (Johnson, JCO 2012)
A double (/triple) hit lymphoma...

...is a DLBCL with a MYC and concurrent BCL2 or BCL6 rearrangement(s)

...may present with the morphology of a DLBCL or a BCLU

...represents in ~ 40 % a transformed follicular lymphoma...

...but is in 60 – 80 % a *bona fide de novo* DLBCL

Patients with DH/TH with MYC/Ig rearrangements have a worse prognosis

Most sensitive assay for detection: break apart FISH probe
HOW TO TREAT A DOUBLE-HIT “DLBCL”?

Retrospective multicenter US analysis

311 patients, median FU 23 months

Median PFS 10.9 months
Median OS 21.9 months

Petrich, Blood 2014
THE MD ANDERSON EXPERIENCE

129 cases treated 2003 - 2013, median FU 18 months (!)

DA-EPOCH-R > standard R-CHOP or other approaches!

**convinced enough to give e.g. DA-EPOCH-R to your next patient?**

*Oki, Br J Haematol 2014*
High-grade B-cell lymphoma – the clinicians view

Estrogen receptors: prognostic & predictive impact

**EBCTCG**
*Lancet 2011*

**ER +**

Benefit from Tamoxifen

**ER -**

Hayes, BCRT 1998
Trastuzumab

HER2 +++ CA

Risk of relapse

▼ 50 %

„simply stunning !“

NEJM 2005; 353: 1673
High-grade B-cell lymphoma – the clinicians view

DA-EPOCH-R for all Burkitt’s?

Event-Free Survival

Overall Survival

Median follow-up: 5 years

Dunleavy, NEJM 2013
CONCLUSIONS

CLINICER OF EINFACH DESPARATE
PATHOLOGISTS TO UNDERSTAND THE CLINICAL REALITY
PATHOLOGISTS TO BE PART WHEN CLINICAL PROTOCOLS ARE DEVELOPED
REPRODUCIBLE AND RELIABLE RESULTS

Bedware of companies (big market, c.f. brast cancer
HER2 and ER probnlem
Get predictive markers

The 2016 revision of the WHO classification

has new lymphoma entities

...and clinicians and pathologists need to talk!
recognizes molecularly defined subgroups

DLBCL treatment is NOT keeping up with progress in mol.

“Bloody old” R-CHOP$_{21}$ = STANDARD FOR MOST DLBCL

Addition of pathway inhibitors has mostly failed (lack of pr.

New treatment concepts are needed...

"Never ignore a gut feeling, but never believe that it's enough.

More must be better is base
High-grade B-cell lymphoma – the clinicians view

**BURKITT’S LYMPHOMA**

*Event-Free Survival*

- Median follow-up: 5 years

*Overall Survival*

- Median follow-up: 5 years

**MYC+ DLBCL**

*EFS*

- 83% (MYC+) vs. 76% (MYC-)

- P=0.59
- Median follow-up 48 months

→ Prospective multi-center validations ongoing

**R-CHOP**

- Blood 2009
• Back-up slides
R-MegaCHOEP: NOT FOR YOUNG / FIT HIGH-RISK PATIENTS

With R-CHOEP-14: 3y EFS 70 % (“excellent!”)

«no need for high-dose consolidation»

Editorial to the DSHNHL 2002-1 trial by B. Coiffier:

Neither of these regimens was standard treatment for patients with DLBCL.

Dense-R-CHOEP not better Schmitz ASH 2015 # 474

→ R-CHOEP-14 (≈ EPOCH-R) = German standard

→ Adding new drugs is the next logical step
NEW WHO CLASSIFICATION: MOST IMPORTANT CHANGES

• **NEW**
  - High grade B-cell lymphomas NOS ≠ B-CLL/CLPD
  - High grade B-cell lymphomas with MYC/BCL2/BCL6

• **Subtype required**
  - GCB vs. ABC

• **Prognostic factors**
  - MYC / BCL2
  - MYC / BCL2 / BCL6

DOUBLE EXPRESSOR LYMPHOMA (DEL)

DOUBLE/TRIPE HIT LYMPHOMA (DHL/THL)

Verify outcome data in prospective clinical trials
NHL-B2 (no R) not confirmed: R-CHOP14 not superior to R-CHOP21 in elderly fit

LNH03-6B (*french*)

End point: EFS

CRUKE/03/019 (*british*)

End point: OS

„no profit for molecular or clinical subtypes“

*Delarue, Lancet Oncol 2013*  
*Cunningham, Lancet 2013*
OTHER KNOWN FACTORS: to be considered…?

For elderly male:
Outcome ↑ by extended rituximab exposure?

Pfreundschuh
JCO 2014

Increased Body Mass Index Is Associated With Improved Survival in United States Veterans With Diffuse Large B-Cell Lymphoma

Carson, JCO 2012
CLINICAL SIGNIFICANCE OF DLBCL SUBTYPES: RETROSPECTIVE

GCB-DLBCL
→ R-DHAP ?

ABC-DLBCL
→ DA-EPOCH-RB ?
→ R-ACVBP ?

Lenz, NEJM 2008; Thieblemont, J Clin Oncol 2011; Dunleavy K, Blood 2009; Molina, JCO 2014
# 2016 WHO classification of Lymphoma

- Mature B-cell neoplasms
  - Chronic lymphocytic leukemia / small lymphocytic lymphoma
  - Monoclonal B-cell lymphocytosis*
  - B-cell prolymphocytic leukemia
  - Splenic marginal zone lymphoma
  - Hairy cell leukemia
  - Splenic B-cell lymphoma / leukemia, unclassifiable
  - Splenic diffuse red pulp small B-cell lymphoma
  - Hairy cell leukemia-variant
  - Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
  - Monoclonal gammopathy of undetermined significance (MGUS), IgM*
  - Mu heavy chain disease
  - Gamma heavy chain disease
  - Alpha heavy chain disease
  - Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
  - Plasma cell myeloma
  - Solitary plasmacytoma of bone
  - Extraosseous plasmacytoma
  - Monoclonal immunoglobulin deposition diseases*
  - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
  - Nodal marginal zone lymphoma
  - Pediatric nodal marginal zone lymphoma
  - Follicular lymphoma
  - In situ follicular neoplasia*
  - Duodenal-type follicular lymphoma*
  - Pediatric-type follicular lymphoma*
  - Large B-cell lymphoma with IRF4 rearrangement*
  - Primary cutaneous follicle center lymphoma
  - Mantle cell lymphoma
  - In situ mantle cell neoplasia*
  - 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 CNS
  - Primary cutaneous DLBCL, leg type
  - EBV positive 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 positive large B-cell lymphoma
  - Plasmablastic lymphoma
  - Primary effusion lymphoma
  - HHV8 positive DLBCL, NOS*
  - Burkitt lymphoma
  - Burkitt-like lymphoma with 11q aberration*
  - High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
  - High grade B-cell lymphoma, NOS*
  - B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Tailoring its heterogeneity: a difficult task in DLBCL

**Morphological**
- centroblastic
- immunoblastic
- anaplastic
- T-cell/histiocyte-rich
- plasmablastic

**Other subtypes**
- EBV+ in elderly
- with chronic inflammation
- lymphomatoid granulomatosis
- HHV8-associated Casteman’s

**Anatomical**
- PCNS
- cutaneous leg type
- Mediastinal / PMBL
- Intravascular
- PEL

**Markers / immunology**
- ALK +
- CD5 +
- CD30 +
- PD-L1 +

**Molecular subtypes**
- GCB, ABC
- PMBL

**Metabolic subtypes**
- OxPhos
- BCR signaling

**Variants**
- interphase DLBCL ↔ HL (mediastinal grey zone)
- interphase DLBCL ↔ Burkitt’s
- Single (MYC +), double & triple hits
- leukemic
MALIGNANT LYMPHOMAS: A PLETHORA OF ENTITIES

~ 80%

Hodgkin lymphoma
Diffuse large B-cell lymphoma
Follicular lymphoma

Marginal zone lymphoma (extranodal)
Marginal zone lymphoma (nodal)
Marginal zone lymphoma (splenic)
CLL
Mantle cell lymphoma

~30 entities (WHO 2008)
~90 % from mature B-cells
~33 % “low-grade”
~70’000 new cases
~19’000 death (www.cancer.org)

Significant heterogeneity!
TAILORING: by treatment options

- **IPI 0 (no bulk)**
  - fit elderly
  - fit late-elderly

- **IPI 1 (± bulk)**
  - unfit, frail

- **IPI ≥ 2**
  - unfit, frail

- **≤ 60 years**
- **60 - 80 years**
- **> 80 years**

- ASCT eligible
- ASCT ineligible
**High-grade lymphomas**

**Powerful clinical significance: (aa)IPI score**

<table>
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<tr>
<th>Risk Group</th>
<th>Number of Adverse Factors*</th>
<th>5-Year Relapse-Free Survival (%)</th>
<th>5-Year Overall Survival (%)</th>
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<td><strong>International Prognostic Index</strong></td>
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<tr>
<td>Low</td>
<td>0 or 1</td>
<td>70</td>
<td>73</td>
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<tr>
<td>Low-intermediate</td>
<td>2</td>
<td>50</td>
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<tr>
<td>High-intermediate</td>
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<tr>
<td>High</td>
<td>4 or 5</td>
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<tr>
<td><strong>Age-adjusted International Prognostic Index</strong></td>
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<td>Low-intermediate</td>
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<td>66</td>
<td>69</td>
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<tr>
<td>High-intermediate</td>
<td>2</td>
<td>53</td>
<td>46</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>58</td>
<td>32</td>
</tr>
</tbody>
</table>

* Adverse risk factors for IPI are: stage III or IV disease, age > 60 years, elevated lactate dehydrogenase (LDH), ECOG performance status ≥ 2, ≥ 2 extranodal sites

# Adverse risk factors for age-adjusted IPI are: stage III or IV disease, elevated LDH, ECOG performance status ≥ 2

Shipp MA, NEJM 1993 & Blood 1994

Ziepert, JCO 2010

1‘062 pts. (MINT, MegaCHOEP, RICOVER)
High-grade lymphomas

**IS R-ACVBP THE NEW STANDARD FOR DLBCL ?**

<table>
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<th>R-ACVBP</th>
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<tr>
<td><strong>R-ACVBP</strong></td>
<td><strong>Doxorubicin</strong></td>
<td><strong>Cyclophosph.</strong></td>
<td><strong>Vindesine</strong></td>
</tr>
<tr>
<td><strong>375 mg/m²</strong></td>
<td><strong>75 mg/m²</strong></td>
<td><strong>1200 mg/m²</strong></td>
<td><strong>2 mg/m²</strong></td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td><strong>Day 1</strong></td>
<td><strong>Day 1</strong></td>
<td><strong>Days 1+5</strong></td>
</tr>
</tbody>
</table>

**Consolidation**

**Concerns:**
- Toxicity
- Feasibility

183). There were five deaths unrelated to lymphoma progression during the treatment period in the R-ACVBP group (three sepsis, one unknown cause) and one intrathecal vindesine injection and three CHOP group (two sepsis and one unknown cause).
## CALGB/Alliance study 50303 Response

### n= 465

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>DA-EPOCH-R</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>89.3%</td>
<td>88.8%</td>
<td>0.983</td>
</tr>
<tr>
<td><strong>CR/CRu</strong></td>
<td>62.3%</td>
<td>61.1%</td>
<td></td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>27%</td>
<td>27.2%</td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>2.6%</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>1.7%</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>6.4%</td>
<td>6.9%</td>
<td></td>
</tr>
</tbody>
</table>

*Wilson et al, ASH 2016, Abstract 469*
## CALGB/ALLIANCE STUDY 50303
### R-CHOP VS DA-EPOCH-R
#### GRADE 3-5 TOXICITIES

<table>
<thead>
<tr>
<th>Event</th>
<th>R-CHOP</th>
<th>DA-EPOCH-R</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment related deaths*</td>
<td>2%</td>
<td>2%</td>
<td>0.975</td>
</tr>
<tr>
<td>ALL Gr 3-4</td>
<td>76.3%</td>
<td>96.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematologic</td>
<td>73.1%</td>
<td>97.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Hematologic</td>
<td>41.3%</td>
<td>70.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ANC</td>
<td>68%</td>
<td>96%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets</td>
<td>11%</td>
<td>65%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>17%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>11%</td>
<td>14%</td>
<td>0.169</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2%</td>
<td>6%</td>
<td>0.011</td>
</tr>
<tr>
<td>Neuropathy - sensory</td>
<td>2%</td>
<td>14%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neuropathy - motor</td>
<td>1%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Wilson et al, ASH 2016, Abstract 469*
DLBCL - diagnostic algorithm

- Diagnose
- Subtyp
  - GCB
  - Non-GCB
  - CD10+/BCL6+/MUM1-
  - CD10-/Bcl6+/-/Mum1+
- Immunphänotyp
- Proliferationsrate
  - Ki67 >80%
  - Bcl2>70%
  - Myc >40%
- MYC/Bcl2 Immun
  - MYC/BCL2+/BCL6*

*: abhängig von der Proteinexpression ev zusätzlich BCL2 oder BCL6 FISH
VALUE OF RADIOTHERAPY – PROBLEMS!

<table>
<thead>
<tr>
<th></th>
<th>LNH03-2B</th>
<th>MInT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-ACVBP (n=196)</td>
<td>8xR-CHOP-21 (n=183)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 (18-59)</td>
<td>48 (19-59)</td>
</tr>
<tr>
<td>Men</td>
<td>116 (59%)</td>
<td>109 (60%)</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>195 (99%)</td>
<td>182 (99%)</td>
</tr>
<tr>
<td>Stage III and IV</td>
<td>115 (59%)</td>
<td>93 (51%)</td>
</tr>
<tr>
<td>LDH &gt;ULN</td>
<td>77 (39%)</td>
<td>89 (49%)</td>
</tr>
<tr>
<td>Bulk ≥10 cm</td>
<td>38 (19%)</td>
<td>45 (25%)</td>
</tr>
<tr>
<td>3-year EFS (%)</td>
<td>81% (75-86)</td>
<td>67% (59-73)</td>
</tr>
<tr>
<td>3-year PFS (%)</td>
<td>87% (81-91)</td>
<td>73% (66-79)</td>
</tr>
<tr>
<td>3-year overall survival (%)</td>
<td>92% (87-95)</td>
<td>84% (77-89)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Pfreundschuh, Lancet Oncol 2011

RT: no published randomized evidence with R-CHOP

Eagerly awaited
GOELAMS 02 03 (ASH`14 # 393)
UNFOLDER (12-ICML # 122)

What is a bulk? (5 or 7.5 or 10 cm?)
Do all patients need radiotherapy, or just PET+?
High-grade lymphomas

BCR MUTATIONS DO NOT PREDICT RESPONSE TO IBRUTINIB

ABC-DLBCL 39%

21%

10%

Ibrutinib

CLL: BTKM in 5/13 pts. refract. to ibrutinib

M. Waldenström (~90% MYD88 M): RR ~80%

HL: active with few M (BCR 20%, BTK 10%)

Treon, NEJM 2015; Woyach, NEJM 2014

Hamadani NEJM 2015

→ Most responses in BCR WT ABC
→ oncogenic BCR signaling by non-genetic mechanisms !?!

Wilson, ASH 2012 & Nat Med 2015

Cheung, ASH 2015 # 2642
TRIALS FOR AGGRESSIVE LYMPHOMAS: RADIOTHERAPY?

UNFOLDER

* DLBCL, 18-60 years, aalPI=0 with bulk or aalPI=1
* 6 x R-CHOP-21 vs. 6 x R-CHOP-14 +/- RT (phase III)

DSHNHL

IELSG-30

* Testicular lymphoma
* 6 x R-CHOP-21, scrotal irradiation, Depocyte, hdMTX (phase II)

Primary endpoint 3 yr PFS
Needs 378 randomised patients for 80% power, p=0.05
Suggests 540 registered patients if 70% PET negative
DLBCL, NOS
- Cell of origin (COO): required
- Distinguish GCB from non-GCB type DLBCL
- Any IHC algorithm accepted (Hans, Visco, Tally...)
- Co-expression of MYC & BCL2: optional (“double-expressors”)

EBV+ DLBCL, NOS
- good news for those that are 50+
- replaces EBV+ DLBCL ”of the elderly”
- Can occur in younger individuals
- ”NOS” to exclude specific EBV+ LBCL (LyG)

EBV+ mucucutaneous ulcer
- new provisional entity
- assoc. with iatrogenic immununsuppression or immunosenescence
• Back-up slides #2
Study Algorithm

Primary endpoint 3 yr PFS

Needs 378 randomised patients for 80% power, p=0.05

Suggests 540 registered patients if 70% PET negative

Rearranged by the presenter
WHAT IS A DOUBLE-HIT (DH) LYMPHOMA?

defined as a \textit{myc} abnormality + another abnormality (\textit{genetic double-hit})

10\% of DLBCLs have a \textit{myc} translocation

DH lymphomas: 2/3 + \textit{bcl-2}; 1/5 \textit{bcl-6}, \textit{rest: triple-hit}

double-protein lymphomas include double-hit cases

but also additional cases (alternative mechanisms leading to overexpression of oncogenes)
### AGGRESSIVE LYMPHOMAS: CURRENT IMPORTANT TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNFOLDER</strong></td>
<td>DLBCL, 18-60 years, aaIPI=0 with bulk or aaIPI=1</td>
</tr>
<tr>
<td><strong>DSHNHL</strong></td>
<td>6 x R-CHOP-21 vs. 6 x R-CHOP-14 +/- RT</td>
</tr>
<tr>
<td><strong>IELSG 30</strong></td>
<td>Testicular lymphoma</td>
</tr>
<tr>
<td></td>
<td>6 x R-CHOP-21, scrotal irradiation, Depocyte, hdMTX (phase II)</td>
</tr>
</tbody>
</table>

Find your patients!
CONCLUSIONS

R-CHOP\textsubscript{21} = STANDARD FOR MOST DLBCLs

Unmet need high-risk, younger DLBCL patients

double-hit lymphomas (\textit{separate entity in new WHO classification, Basel!})

 Awaited R-CHOP vs. DA-EPOCH-R (ASH 2016 ?)

UNFOLDER & GOELAMS 02 03 & IELSG 37
de-escalation (FLYER: 4 x R-CHOP for low-risk IPI < 60)

Challenge improving results of \textit{bloody old} R-CHOP

incorporation of new drugs (XR-CHOP)

confirm prospectively what is seen retrospectively

dealing with the lack of predictive markers

& \textit{rarer} entities / populations

More must be better is based on a gut feeling...

"Never ignore a gut feeling, but never believe that it's enough."
High-grade lymphomas

Treating aggressive lymphomas in the CNS…
…needs our collaboration

IELSG 42
An international phase II trial assessing tolerability and efficacy of sequential Methotrexate-Aracytin-based combination and R-ICE combination, followed by high-dose chemotherapy supported by autologous stem cell transplant, in patients with systemic B-cell lymphoma with central nervous system involvement at diagnosis or relapse (MARIETTA regimen)
EudraCT: 2014-003031-19

CH: Zürich (lead EC), Bern, Lucerne, Aarau, Bellinzona

IELSG43 - MATRix
High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial
EudraCT- Number: 2012-000620-17

CH: Bern (lead EC), Zürich, Aarau, Lausanne, Bellinzona

Rare! Consider referring your patients!