Identifying High-Risk DLBCL and Management Implications

Timothy Voorhees, MD, MSCR
Assistant Professor of Internal Medicine – Clinical
The James Comprehensive Cancer Center
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University Wexner Medical Center

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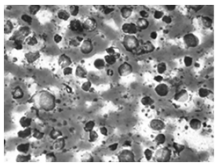
Objectives

- Methods of detecting high-risk diffuse large B-cell lymphoma
  - Prediction Models
  - Cell of Origin and Molecular Risk
  - Imaging
- Management decisions
  - Selection of Appropriate Therapy
  - Future Directions

Defining Diffuse Large B-cell Lymphoma

DLBCL

- Incidence 8/100,000
- Median age 70 years
- B symptoms (weight loss, night sweats, fatigue, poor appetite)
- Architecture disruption of lymph node with large, malignant B-cells



https://commons.wikimedia.org/wiki/File:Large_b_cell_lymphoma_-_cytology_small.jpg

Long term outcomes in DLBCL

R-CHOP chemotherapy has been standard for >15 years

- Rituximab + Doxorubicin, Cytoxan, Vincristine, Prednisone
- R-CHOP vs CHOP Phase III study
- 10-year survival
  - R-CHOP – 43.5%
  - CHOP – 27.6 %

Coiffier et al, Blood, 2010

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Revised International Prognostic Index

Risk Factors	R-IPI points
Age >60	1
Stage III/IV	1
Elevated Lactate Dehydrogenase	1
Performance status ≥ 2	1
Extranodal Disease	1

Risk Group	IPI factors	4-year PFS	4-year OS
Very good	0	94%	94%
Intermediate	1-2	80%	79%
Poor	3-5	53%	55%

Sehn et al, Blood, 2007

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Cell of Origin

DLBCL can be subtyped by Cell of Origin:

- B-cell maturation at time of transformation
- Germinal Center DLBCL vs non-germinal center DLBCL
- Based in gene expression differences
- Gene expression assays are not available clinically
- Hans criteria (clinically available) - estimate gene expression

Hans et al, Blood, 2004

Cell of Origin – Hans Criteria

Germinal Center (GCB) type

- CD10(+)
- CD10(-), BCL6(+), MUM1(-)

Non-Germinal Center (non-GCB) type

- CD10(-), BCL6(+), MUM1(+)
- CD10(-), BCL6(-)

Cell of Origin	5-year OS
GCB	~70%
Non-GCB	~30%

Hans et al, Blood, 2004

Double Expressor and Double Hit

Myc

- Oncogene - activates expression of proliferation factors
- Overexpressed or genetic translocation

BCL2 and BCL6

- Both stop apoptosis and promote cell survival
- Overexpressed or genetic translocation

Hans et al, Blood, 2004

Double Expressor and Double Hit

Double Expressor

- Myc + BCL2 overexpression

Double Hit

- MYC genetic translocation
- BCL2/BCL6 translocation

	5-year OS
DLBCL	70%
Double Expressor	36%
Double Hit	27%

Johnson et al, JCO, 2012

Genomic Drivers - DLBCL

Large scale genomic sequencing

- 1001 DLBCL patients sequenced, whole exome sequencing
- Alterations associated with increased risk of death included:
  - *CD79B*, *MYC*, *ZFAT*, *CDKN2A*, *PAX5*, *BTG1*, *KLHL14*, *NCOR1*, and NFKBIA
- Comparing clinical IPI risk and genomic risk, no significant difference

Reddy et al, Cell, 2017

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Metabolic Tumor Volume (MTV)

Calculated from ^{18}F-FDG PET/CT scans by summing the volumes of all lymphomatous lesions

- 114 newly diagnosed DLBCL, divided into quartiles
  - 3-year OS: 93%, 84%, 78%, 59%
- Combining MTV with molecular risk (double expression)
  - 3-year OS: ~80% (MTV low, no double expression), ~60% (MTV high, no double expression), 0% (MTV high and double expression)

Sasanelli et al, Eur J Nuc Med Mol Imaging, 2014
Sehn et al, Clin Cancer Research, 2016

Summary - Defining High Risk DLBCL

- R-IPI risk score provides a good estimate of survival
- Cell of origin, double expression, and double-hit play roles in predicting survival
- Genetic alterations can predict survival but not available in clinic yet
- High volume disease is an independent risk factor which may or may not be captured in the IPI or pathologic features

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- Rituximab + Doxorubicin, Cytoxan, Vincristine, Prednisone
- Rituximab – CD20 antibody, antibody dependent cell cytotoxicity. Depends on natural killer cells and others
- Chemotherapy: inhibits cell cycle through multiple mechanisms
- 10-year survival: R-CHOP – 43.5%

Coiffier et al, Blood, 2010

More Chemo = Better Chemo?

R-CHOP vs dose adjusted R-EPOCH **(all DLBCL patients)**

- Rituximab + Doxorubicin, Cytoxan, Vincristine, Prednisone
- Rituximab + Etoposide, Doxo, Cytoxan, Vincristine, Pred
- Toxicity
  - Grade 3-5 toxicities – 78% RCHOP; 98% REPOCH
  - Grade ≥3 Febrile neutropenia – 18% vs 35%
  - Grade ≥3 Neuropathy – 3% vs 18.6%

Barlett et al, JCO, 2019

More Chemo = Better Chemo?

R-CHOP vs dose adjusted R-EPOCH **(all DLBCL patients)**

- 5-year PFS – 66% R-CHOP vs 68% R-EPOCH
- 5-year OS – 78% R-CHOP vs 78% R-EPOCH
- Subgroup analyses?
  - By double expressor – no difference
  - By R-IPI 1-2 vs 3-5 – potential trend towards improved PFS with R-EPOCH, but due to toxicity, not recommended

Bartlett et al, JCO, 2019

More Chemo = Better Chemo?

R-CHOP vs dose adjusted R-EPOCH **(Double Hit)**

- There is no randomized data to compare
- Limited prospective data
  - 19 Double Hit patients treated with R-EPOCH
  - 2-year OS: ~70%
- Retrospective data
  - 2-year OS: ~75%

Dunleavy, Lancet Haematol, 2014
Oki et al, BJH, 2014

Challenges To R-CHOP

REMoDL-B: phase III V-R-CHOP vs R-CHOP

- V-R-CHOP: Bortezomib + R-CHOP
  - Stratified by Cell of Origin – gene expression profiling
  - >1000 patients underwent gene expression profiling
  - 244 ABC type, 475 GCB type, 199 unclassifiable
  - 30-month PFS
    - All patients: 70% R-CHOP; 75% V-R-CHOP; p – 0.18

Davies et al, Lancet Oncol 2019

Challenges To R-CHOP

PHOENIX: phase III Ibrutinib-R-CHOP vs R-CHOP

- Stratified by Cell of Origin – Hans criteria – non GCB
- 836 patients underwent randomization
- There was no difference in EFS – HR 0.93, p – 0.59
- There was no difference in OS – HR 0.99, p – 0.96

*** Subgroup analyses did show benefit in patients <60 years leading to hypothesis that toxicity from Ibrutinib may limit benefit in older patients

Younes et al, JCO 2019

Challenges To R-CHOP

ROBUST: phase III Len-R-CHOP vs R-CHOP

- Lenalidomide 15mg daily; day 1-14 every 21 days
- Selected by Cell of Origin – gene expression profiling
- 570 patients randomized
- Len-R-CHOP did not improve PFS; HR 0.85, p – 0.29

*** Possibility that “highest risk” patients cannot wait for gene expression profiling.

Nowakowski et al, JCO 2021

Challenges To R-CHOP

POLARIX: phase III Polatuzumab-R-CHP vs R-CHOP

- Polatuzumab vedotin – CD79b antibody drug conjugate
- Selected by IPI score 2-5; 879 patients randomized
- Pola-R-CHP did improve PFS; HR 0.72, p – 0.02
- 2-year PFS: 76.7% Pola-RCHP vs 70.2% R-CHOP
- No overall survival benefit

*** First study to “beat” R-CHOP in DLBCL

Tilly et al, NEJM 2021

Challenges To R-CHOP

POLARIX: phase III Polatuzumab-R-CHP vs R-CHOP

- Still some debate surrounding magnitude of 6% PFS benefit at 2 years, more to come over time
- Toxicity: very similar to R-CHOP. More neutropenia – all patients will receive Neulasta
- Subgroup analyses: use with caution
  - Largest benefit seen in IPI 3-5, ABC subtype, non-bulky disease, patients >60 years

Tilly et al, NEJM 2021

Summary - Defining High Risk DLBCL

- R-CHOP has been standard of care for decades
- R-EPOCH is more toxic, but no better in all DLBCL
- R-EPOCH is likely beneficial in Double-Hit DLBCL
- Multiple regimens have failed to beat R-CHOP in DLBCL
- Pola-R-CHP is the first to show a PFS benefit, though no OS benefit at this time

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Future Directions

Ongoing Clinical Trials Of Interest:

- Additional Antibody Therapies
- Chimeric Antigen Receptor T-cell Therapy
- Bi-Specific Antibody Therapy

Future Directions

Additional Antibody Therapies:

- Phase II: Zilovertamab vedotin + R-CHP
  - ROR1 antibody drug conjugate
- Phase III: Tafasitamab + R-CHOP vs R-CHOP
  - CD19 Antibody

Future Directions

Chimeric Antigen Receptor T-cell (CAR-T) therapy:

- CAR-T cell therapy = modified T-cells from patient to target antigen on tumor. CD19 is the most common target.
- CAR-T cell therapy beneficial in 2nd line treatment for DLBCL.
- ZUMA-12:
  - Phase II study – front-line CAR-T for double hit and IPI $\geq$3
  - Prelim response rate: 40 patients, 89% responded, 78% complete response

Neelapu et al, Nat Med 2022

Future Directions

Bi-specific Antibody Therapies:

- Antibodies with target (CD20) and immune activation (CD3)
- Phase II: Glofitamab + R-CHOP
  - CD20 x CD3 bi-specific antibody
- Phase II: Epcoritamab + R-CHOP
  - CD20 x CD3 bi-specific antibody

Summary – Future Directions

- Multiple studies are ongoing to test new immunotherapies combined with R-CHOP or Polatuzumab-R-CHP
- CAR-T cell therapy and Bi-specific antibody therapies are the most promising at this time for continued improvement in outcomes
- Once improvement can be shown, we will may to consider de-escalation of chemotherapy portions of novel regimens to limit toxicity

Indolent B-cell Lymphomas

Yazeed Sawalha, MD
Assistant Professor
Department of Internal Medicine
Division of Hematology
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University Wexner Medical Center

Outline

- Overview of lymphoma subtypes
- Indolent B-cell lymphomas
  - Follicular lymphoma
  - Marginal zone lymphoma
  - Waldenström macroglobulinemia

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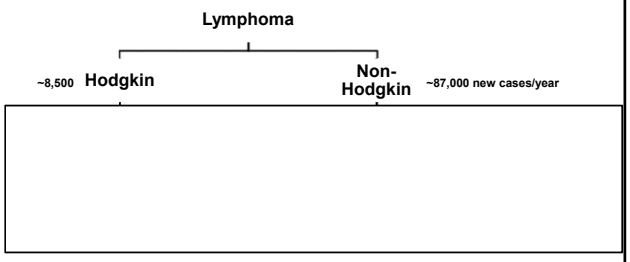
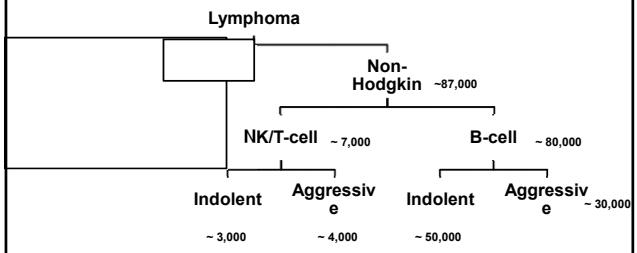
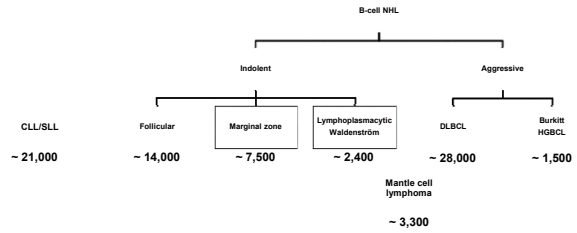
Lymphoma Classification (Simplified)



Lymphoma Classification (Simplified)



Lymphoma Classification (Simplified)



Teras et al. CA Cancer J Clin. 2016

Indolent B-cell NHL

- Lymphomas that typically grow slowly (over many months to years)
- Most patients present at advanced stage
- Generally considered incurable
- Relapsing and remitting course
- Treatment is generally indicated to control symptoms and prevent end-organ damage
- *Most* patients can anticipate a normal life expectancy
- Carry a risk of transformation to a more aggressive lymphoma

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Diagnosis/Staging

- Fine-needle aspirate is inadequate for initial diagnosis
- Excisional biopsy is recommended
- Core-needle biopsy may suffice when excision not feasible

- CBC, CMP, LDH, HIV, and Hepatitis panel
- PET/CT for follicular lymphoma +/- marginal zone lymphoma
- CT scans for lymphoplasmacytic lymphoma +/- marginal zone lymphoma
- Bone marrow biopsy in selected patients
- Serum monoclonal protein

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Diagnosis

- Based on morphology, immunophenotype, and molecular genetics

	CD5	CD10	CD20	CD23	CD138
SLL/CLL	+	-	+ (DIM)	+	-
FL	-	+	+	-/+	-
MZL	-	-	+	-/+	-
LPL	-	-	+	-	+
MCL	+	-	+	-	-

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Molecular Alterations in Indolent NHL

Histologic Type	Alteration	Cases Affected	Proto-Oncogene Involved	Mechanism of ProtoOncogene Activation	Proto-Oncogene Function
FL	t(14;18)	90%	BCL-2	Transcription deregulation	Negative regulator of apoptosis
MALT lymphoma	t(11;18)	50%	API_2/MLT	Fusion protein	API_2 has antiapoptotic activity
LPL	MYD88 L265P mutation	95%	MYD88	Activation	B-cell signaling
MCL	t(11;14)	70%	Cyclin D1	Transcription deregulation	Cell cycle regulator

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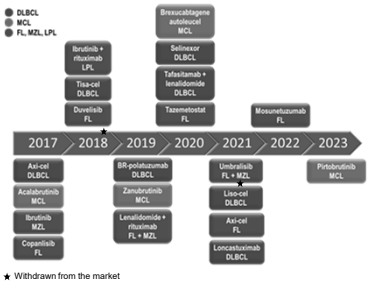
Therapeutic Advances in B-cell Lymphomas



Follicular Lymphoma

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Follicular Lymphoma – Clinical Presentation

- Majority present with painless lymphadenopathy, may wax and wane
- 80-85% present with advanced-stage disease (stage III/IV)
- B symptoms in 20%
- Very heterogenous disease

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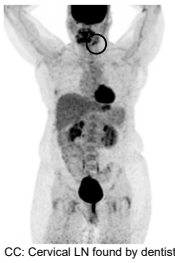
Follicular Lymphoma – Clinical Presentations



CC: Cervical LN found by dentist

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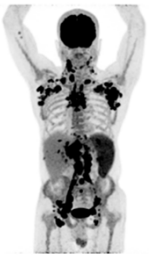
Follicular Lymphoma – Clinical Presentations



CC: A lump under left armpit

Follicular Lymphoma – Clinical Presentations

CC: Abdominal pain
and B symptoms

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Indications for Treatment (GELF Criteria)

- Involvement of at ≥3 nodal sites (each with a diameter >3 cm)
- Any nodal or extranodal mass ≥7 cm in its greater diameter
- B symptoms
- Splenomegaly
- Pleural/peritoneal effusion
- Cytopenias (leukocytes <1.0 × 10^9/L and/or platelets <100 × 10^9/L)
- Leukemia (>5.0 × 10^9/L malignant cells)

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FL – First-line Treatment

- XRT for limited-stage disease in a peripheral location (e.g., inguinal lymph nodes)
- Observation (watch-and-wait) for asymptomatic patients with low-tumor burden
- When systemic treatment is indicated, options include:
  - **Rituximab monotherapy:** Favored for symptomatic low-tumor burden or unfit patients
  - Anti-CD20 monoclonal antibody (**rituximab, obinutuzumab**) + chemotherapy (**bendamustine, CHOP**) +/- maintenance
    - Favored for fit patients with bulky/symptomatic disease
  - **Lenalidomide + anti-CD20 monoclonal antibody (rituximab, obinutuzumab)**
    - "non-chemo" option - Patient/physician preference

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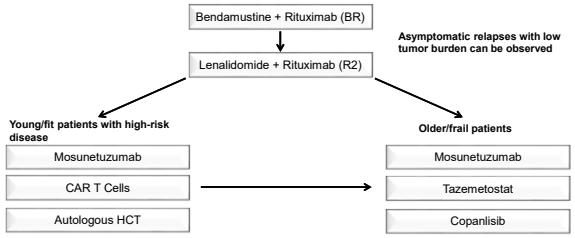
Approach to the Treatment of High-tumor Burden FL



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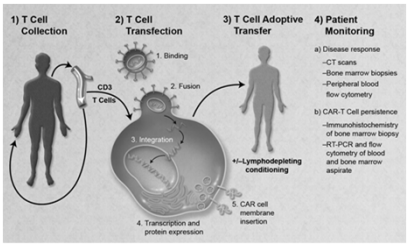
Chimeric Antigen Receptor (CAR) T cells



Jacobson C & Ritz J, Blood (2011) 118 (18): 4761–4762

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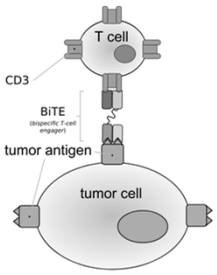
Bispecific Antibodies

- Small linker peptides connecting two different single-chain variable fragments with one fragment designed to bind to CD3 on T cells and the other to a tumor associated antigen
- The simultaneous binding of CD3 on T cells and the tumor associated antigen triggers T-cell mediated cytotoxicity of the malignant cell.



https://commons.wikimedia.org/wiki/File:BiTE_antibody_01.svg

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Marginal Zone Lymphoma

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Subtypes

- Extranodal (MALT)
  - ~ Two-thirds of cases
  - At any extranodal site, usually in the context of chronic antigenic stimulation
  - Stomach, ocular adnexa, lung, salivary glands, …
  - RT is very effective for localized disease
- Splenic, ~ 20%
  - Lymphocytosis is common
- Nodal, ~ 10%

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Infections/Inflammation

- **Helicobacter pylori → Gastric**
- Chlamydia psittaci → Ocular
- Campylobacter jejuni → Immunoproliferative small intestinal disease (IPSID)
- Borrelia afzelii → Skin
- Achromobacter xylosoxidans → Pulmonary
- Hepatitis C → Splenic

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Gastric MALT Lymphoma

- Most common subtype, 30-50% of all cases
- Associated with H. pylori
- Present with local symptoms
- **If H. pylori positive**, preferred treatment is H. pylori eradication followed by surveillance
- **If H. pylori negative and localized disease (stage I-II)**, preferred treatment is RT with curative intent

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MZL – Treatment Options

- Rituximab monotherapy
- Rituximab + chemotherapy (bendamustine)
- Targeted/novel agents:
  - Lenalidomide + rituximab
  - BTK inhibitors (zanubrutinib)
  - PI3K inhibitors (copanlisib)

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Case Presentation

- A 53-year-old female presented with headache, vision blurring, and confusion.
- Exam was notable for hemorrhagic retinopathy.
- Labs:

CBC: Normocytic anemia (Hb 8.6 g/dL)

Bilirubin Total <1.5 mg/dL	0.2
ALP 32 - 126 U/L	42
ALT 9 - 48 U/L	12
AST 14 - 40 U/L	21
Total Protein 6.4 - 8.3 g/dL	>24.0 ^

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IGM 45 - 281 mg/dL	9,160 ^
Monoclonal 1 <=0.0 mg/dL	7,198.0 ^
Serum Immunofixation	IgM kappa monoclonal protein is present.
Viscosity, Serum 1.5 - 1.9 rel to H2O	13.0 ^

Bone marrow biopsy confirmed Waldenström Macroglobulinemia

Lymphoplasmacytic Lymphoma

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

- LPL + IgM monoclonal protein + BM involvement = Waldenström Macroglobulinemia
  - WM accounts for 95% of LPL cases
- Symptoms/signs due to
  - Organ infiltration: bone marrow, splenomegaly, lymphadenopathy, extranodal involvement
  - IgM-related:
    - Hyperviscosity
    - Peripheral neuropathy 25-50%
    - Cryoglobulinemia ~ 10%
    - Cold agglutinin hemolytic anemia ~ 10%
  - AL amyloidosis

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LPL - Treatment

- ~25% asymptomatic and can be observed
- The level of M protein alone is not an indication to start treatment
  - Carefully monitor patients with IgM > 5,000 – 6,000
- Plasmapheresis when immediate reduction in IgM is needed
  - Hyperviscosity, symptomatic cryoglobulinemia, severe hemolysis from cold agglutinin disease
- Preferred treatment for symptomatic patients is chemotherapy (BR) or a BTK inhibitor (zanubrutinib, ibrutinib)

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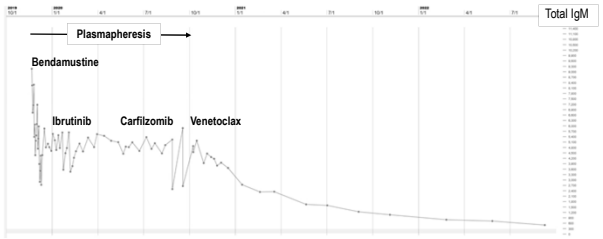
Case Presentation



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