Identifying High-Risk DLBCL and Management Implications

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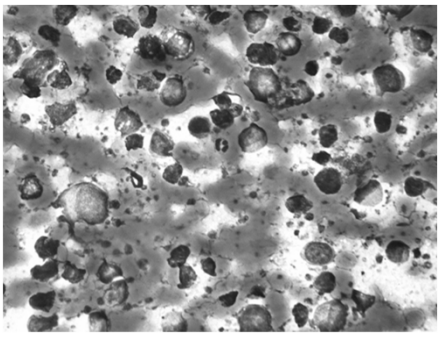
Objectives

- 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
Sarkozy 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: <u>use with caution</u>
  - 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 ≥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

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Outline

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

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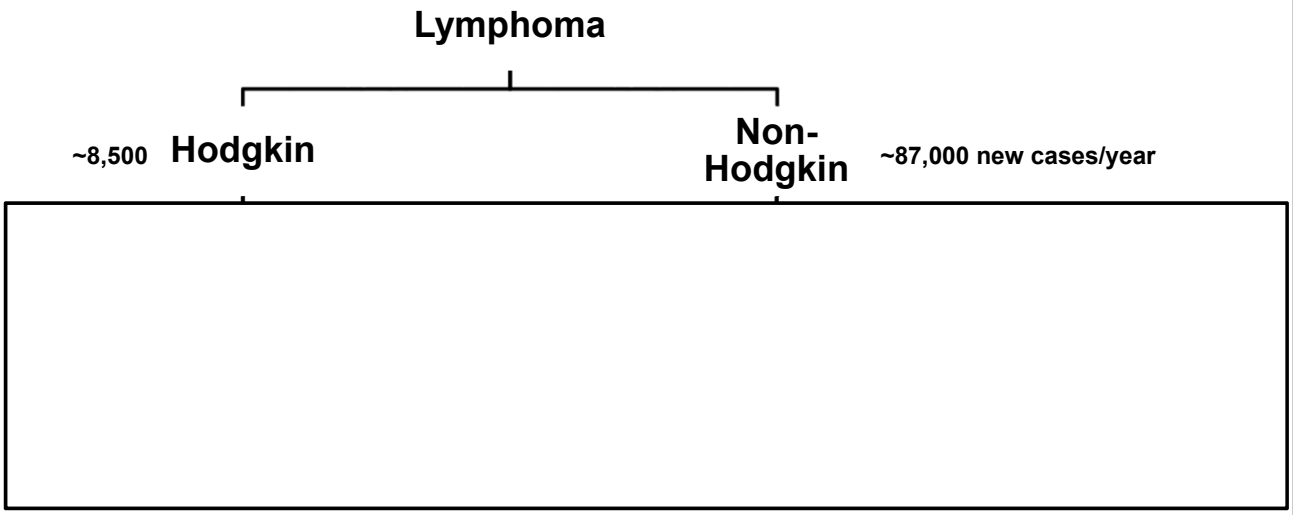
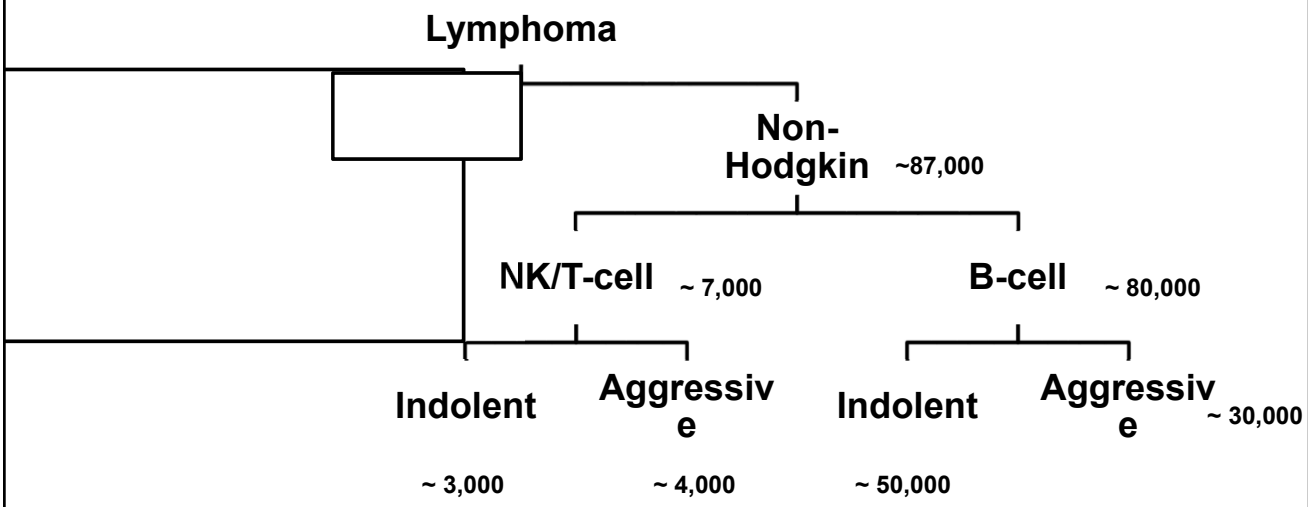
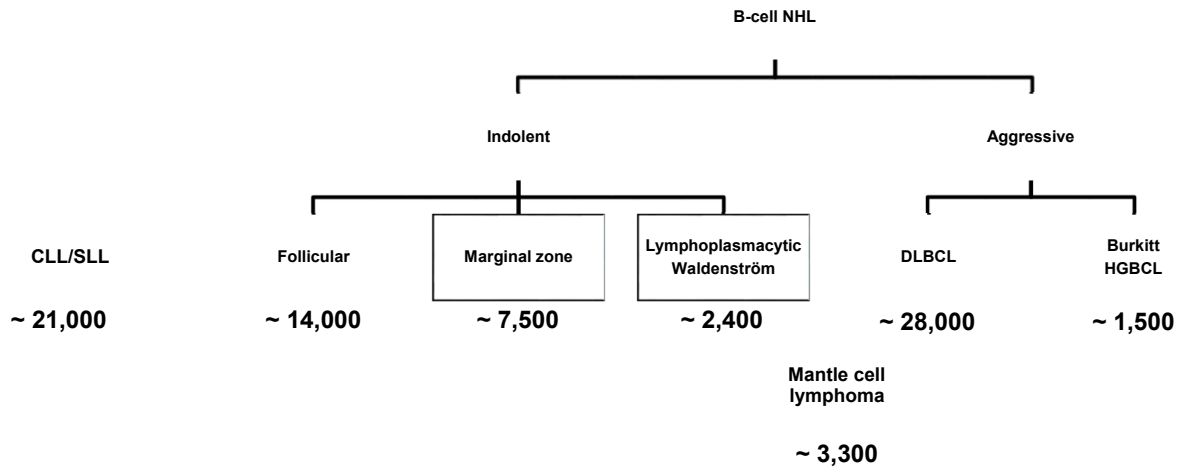
Lymphoma Classification (Simplified)



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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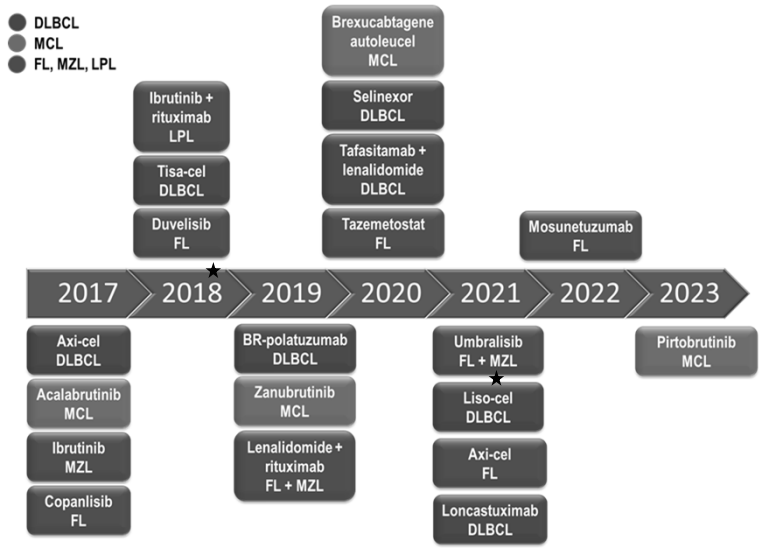
Therapeutic Advances in B-cell Lymphomas



★ Withdrawn from the market

Follicular Lymphoma

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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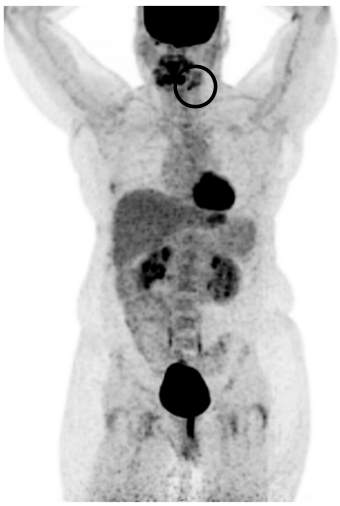
Follicular Lymphoma – Clinical Presentations



CC: Cervical LN found by dentist

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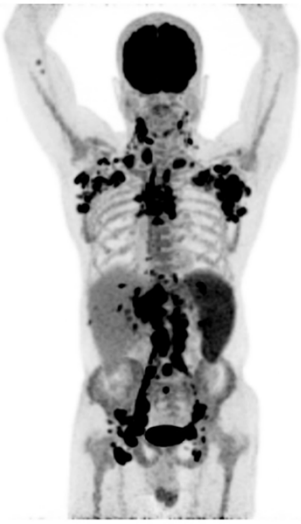
Follicular Lymphoma – Clinical Presentations



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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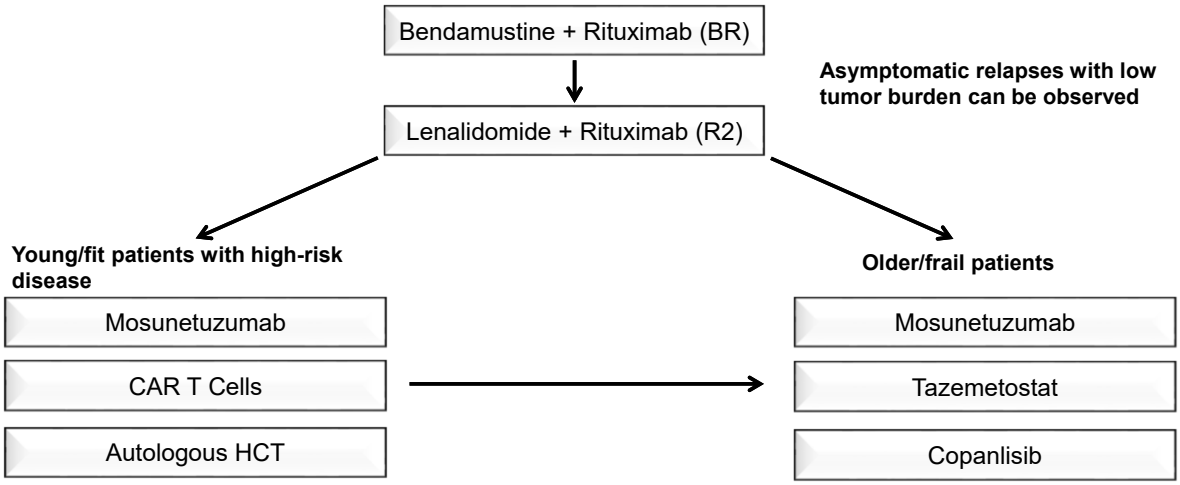
Approach to the Treatment of High-tumor Burden FL



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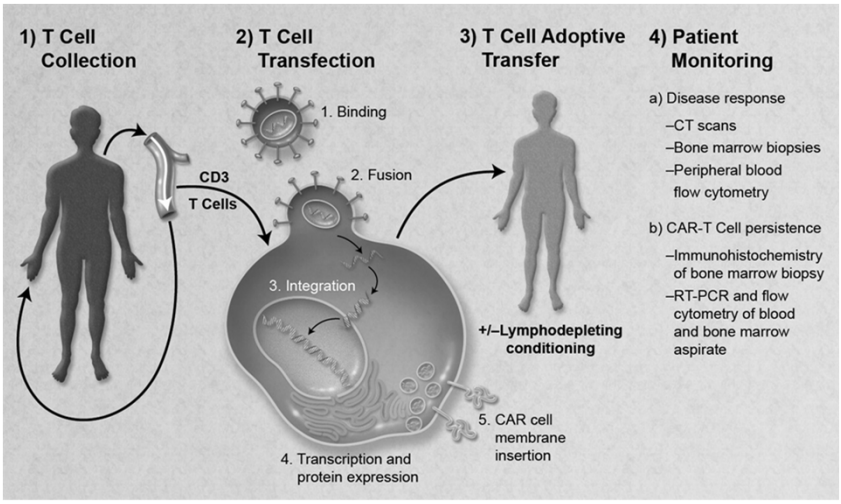
Chimeric Antigen Receptor (CAR) T cells



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

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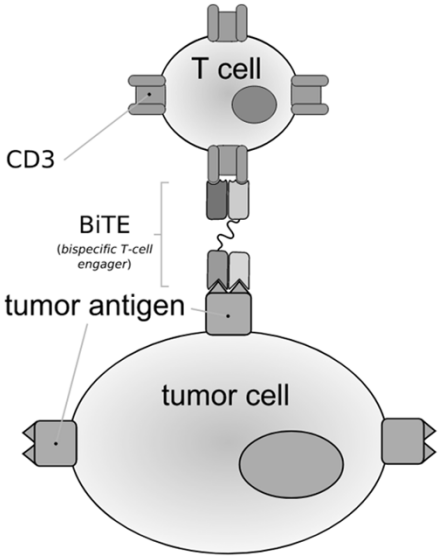
Bispecific Antibodies

- 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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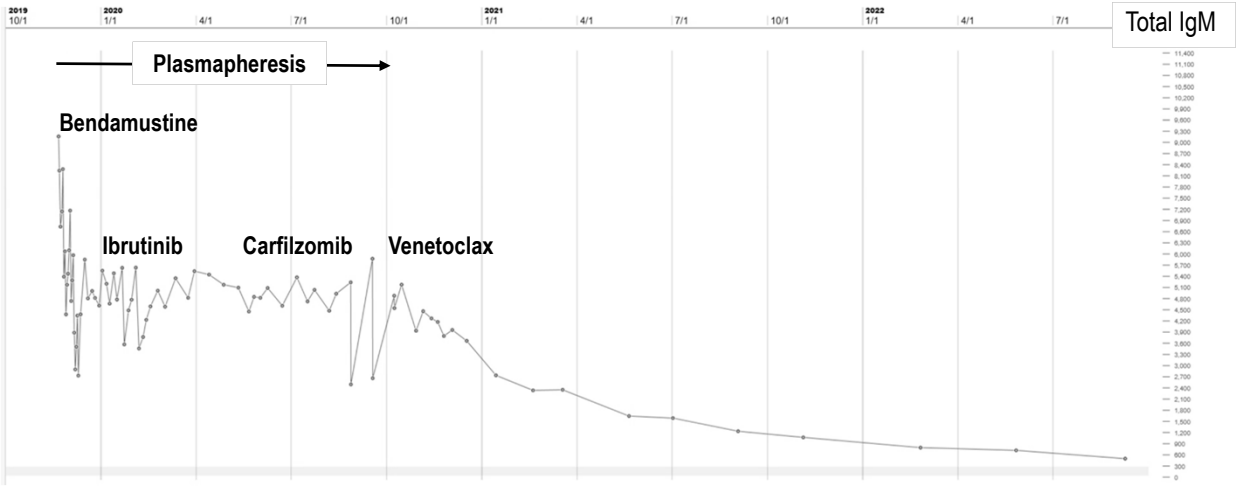
Case Presentation



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