Aggressive Non-Hodgkin lymphoma 2017: Are targeted therapies really helping?

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Objectives

• Review the pathophysiology of diffuse large B cell lymphoma (DLBCL)
• Describe the expected outcome of current treatment for DLBCL
• Review recent important clinical trials in DLCBL
• Identify potential new targets of treatment and research for DLBCL available and how new treatments will impact management
Background

- DLBCL is the most common NHL in the US
- About 25% of all NHL in the US
- 25,000-30,000 cases per year
- Median age about 60, a little more common in men
- About 60% present with advanced disease
WHO 2016 Classification Mature B cell neoplasms

- CLL/SLL
- Monoclonal B cell lymphocytosis
- B cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Lymphoplasmacytic lymphoma
  - Waldenstrom macroglobulinemia
- MGUS
- Heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraskeletal plasmacytoma
- Monoclonal Ig deposition disease
- MALT lymphoma

- Nodal marginal zone lymphoma
- Follicular lymphoma
- Pediatric-type follicular lymphoma
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- Diffuse large B cell lymphoma
  - Germinal center B cell type
  - Activated B cell type
- T-cell rich large B cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL leg type
- EBV+ DLBCL
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B cell lymphoma
- Primary ALK+ large B cell lymphoma
B Cell Development

- **t(11,14)**
- **MZL bcl-10**
- **BL c-myc**
- **B Cell Development**

**Key Points**
- **Primary repertoire**
- **Germinal center**
  - Pre-clonal selection
  - Beneficial mutations and affinity maturation
- **Somatic hypermutation**
- **Clonal expansion**
  - Antigen stimulation
- **Secondary repertoire**
  - Immunosecretory disorders MM (MGUS)
- **Cell Types**
  - **B cell**
  - **T cell**
  - **FDC**
  - **CLL (mutated) (ABC-DLBCL)**
  - **FL (GC-DLBCL)**
  - **Plasma cell**
  - **Plasmablast**
  - **Memory B cell**

**Proteins**
- **M2L bcl-10**
- **BCL-10**

**Processes**
- **Apoptosis**
- **Differentiation**
- **Selection and class switching**
- **Deleterious mutations**
## DLBCL Prognosis

- **International prognostic index**
- APLES; Age, Performance status, LDH, extranodal >1, Stage III or IV

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<th>CR rate,</th>
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<td>High risk</td>
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DLBCL outcome is dependent upon pathology
Germinnal Center GC versus Activated B Cell ABC

IHC defined: CD10, Bcl-6, and MUM-1
Diffuse large B cell NHL

3 subtypes:
3 pathways to Malignant transformation

What pathways are we targeting with chemotherapy?
DLBCL prognosis is worse with “double hit”

- myc gene translocations are seen in aggressive Burkitt lymphomas
- myc gene translocations combined with gene rearrangements in bcl-2 and/or bcl-6 (“double or triple hit”) determined by cytogenetics or FISH are present in up to 10% of DLBCL and have had worse outcome: PFS 11 months, OS 22 months. Most have GCB phenotype.
- These patients usually present with advanced stage and high IPI disease, often with extranodal disease, including + marrow in 50%
- Immunohistochemistry for myc, bcl-2, and bcl-6 has shown about 25% have 2 or 3 + markers; less than half will show translocations (“double expressors”) and as a group have had better outcomes than “double hit”: 3 yr OS 50%. Most double expressors are ABC subtype of DLBCL
CHOP as the standard treatment of DLBCL

NEJM 328:1002-1008, 1993
How to improve upon CHOP

• Better understanding of the disease
  • Are there some groups that do better or worse based upon biomarkers?
  • Identify new or different targets of treatment
• Better drugs or drug combinations
Cell surface antigens present on lymphocytes: potential targets for therapy in lymphomas
The value of antibody treatment in DLBCL

Rituximab

Survival using chemotherapy with or without rituximab

JCO 23(22):5027, 2005
Post chemotherapy monoclonal antibody strategies

- Autologous transplant patients have high relapse rates, so evaluations in this population seemed appropriate and likely to be beneficial
  - Anti-CD19 MoAbs were studied post autologous transplants in the 1990s and showed no benefit
  - Anti-CD20 MoAb rituximab was evaluated in the post transplant setting in the Coral trial: 4 yr EFS 52% vs 53% with or without rituximab
  - Anti-CD20 MoAb radiommuno-conjugate with transplant Iodine-131 Tositumomab BMT CTN 0401: (-) Bexxar: 2 yr PFS 49% OS 66% (+) Bexxar PFS 48% OS 61% J CO 31:1662; 2013
Standard DLBCL population

- 15% to 25% are refractory to any chemotherapy
- 5% PR patients
- 20% to 30% relapses

We need randomized studies on these selected groups of patients

- 50% to 60% are already cured with previous chemotherapy (R-CHOP)
- We will never improve those cure patients

Hematology
ASH Ed 2016
p. 367
DLBCL: Strategies to improve / R-CHOP

- FOCUS ON
  1 ASCT
  2 New Combos
  3 Immune tx

- "More" chemo
- No cycles / 6 vs 8 cycles
  RICOVER trial (q2kws)
- Dose-intensity
  R-CHOP-14 vs 21
- Continuous infusion
  R-EPOCH
- Consolidation w/
  DI / HDT-ASCT upfront
- Prediction response on PET
- Pts stratification ++
- New combinations / R-CHOP + X
- Revisit maintenance strategies
Does high dose chemotherapy and autologous stem cell transplant improve outcome in DLBCL?

- Four randomized trials between standard and high dose chemotherapy have been reported, all show no benefit of transplant treatment.

- However, 3 of the 4 trials show EFS and/or OS in retrospective analysis for intermediate or high risk patients (IPI):
  - GELA LNH87-2: 8 yr DFS 55% vs 39% OS 64% vs 49% p<0.04  *JCO 18:3025; 2000*
  - SWOG 9104: 2 yr OS 83% vs 63%  *NEJM 369:1681-9;, 2013*
  - GOELAMS 075 trial: 3 yr EFS 76% vs 64% OS 91% vs 77%  *JCO 29(abs 8003);2011*
  - NCCN 2B recommendation for select high risk patients DLBCL consider autologous transplantation as consolidation in CR1
Better chemotherapy or better anti-CD20 MoAb?
Better than R-CHOP?

• Single center data suggested that **R-EPOCH** had higher response rates in DLBCL: phase 3 study comparing it to **R-CHOP**. CALGB B5030 trial USA: ASH 2016. No improvement.

• In CLL and FL, **obinutuzumab**, appears more potent than rituximab: trial of **R-CHOP vs G-CHOP**. GOYA phase III trial. ASH 2016. No improvement.
Strategies to add something to R-CHOP or give something after R-CHOP (maintenance)

• Neither adding chemotherapy to R-CHOP or giving R-CHOP differently (every 14 days) has shown benefit.
• ABC and GCC DLBCL have different mechanisms of malignant growth and development—are the opportunities to target these differently?
• From double hit lymphomas, is it possible to target myc, bcl-2, or bcl-6?
• Treating after remission is obtained in high risk populations to eliminate residual disease is very attractive—what can we best target?
• Do you need to target anything, or can you just try to manipulate the immune system using immunomodulatory strategies?
Trials of targeted therapy in DLBCL

- **B cell receptor pathway**
  - BTK inhibitors
  - PI3 Kinase inhibitors
  - PKC inhibitors
  - Syc inhibitors
  - AKT inhibitors
  - mTOR inhibitors

- **Constitutive activation pathway**
  - NF-kB inhibitors
  - CARD10 activation

- **Epigenetic or histone modification**
  - HDAC inhibitors
  - HMA’s

- **Cell cycle activation pathway**
  - Bcl-2 inhibitors
  - Myc inhibitors (BET)

- **Block terminal B cell differentiation**
  - Bcl-6 inhibitors
More active in GCB:
- Idelalisib: PI3K
- BET/myc inhibitors
- Everolimus: mTOR
- EZH2 inhibitors

More active in ABC:
- Bortezomib: NF-κB
- Ibrutinib: BCR, NF-κB
- Lenalidomide: IRF4
Selected results of targeted therapy in DLBCL

• Lenalidomide
  • 40 refractory patients: IHC showed 23 GBC 17 ABC. ORR 9% vs 53%. Cancer 117:5058, 2011
  • 17 relapsed patients: lenalidomide + bendamustine 41% RR, 38% PFS Leuk Lym 35:2508; 2014
  • R2-CHOP Phase 2: 64 patients. 98% RR, 80% CR. 2yr EFS 59%. Outcome the same for GCB and ABC subtypes (overcame the negative ABC type) JCO 33:3215, 2015
  • ROBUST trial R-CHOP vs R2-CHOP in ABC DLBCL clinical trial started 2015
  • REMARC +/- maintenance len in elderly pt: PFS at 40 mo favors maintenance Blood 2016 128:471

• Bortezomib
  • 40 newly diagnosed patients RCHOP + B: 100% RR, 80% CR, 2 yr PFS 64% JCO 29:690, 2011
  • 164 newly diagnosed non-GCB phase II randomize R-CHOP vs. VR-CAP same RR, EFS Blood 126:1893, 2015
  • R-CHOP vs BR-CHOP PYRAMID Phase II trial in 183 non-GCB newly diagnosed patients. RR 98% vs 96%, 2y PFS 78% vs 82%. ASH 2015
Selected results of targeted therapy in DLBCL 2

- Enzastaurin (PKC inhibitor) maintenance post R-CHOP in high risk disease: Phase 3 trial 758 patients 4 yr DFS 70 vs 71%.  
  JCO 34:2484, 2016

- Everolimus (mTOR inhibitor) + Rituxan in 26 relapsed patients: 38% RR, 13% CR.  
  Hematological 98:615, 2013

- Panobinostat (HDAC inhibitor) phase 2 +/- Rituxan: 40 relapsed/refractory/transformed patients. 28% RR, MEF2B associated with response  

- Venetoclax (bcl-2 inhibitor) in 34 relapsed/refractory patients. 18% response rate single agent.  
  JCO 35:826, 2017

- Phase 2 trial of DA-R-EPOCH + venetoclax in aggressive BCL started Jan 2017
Selected results of targeted therapy in DLBCL 3

- Ibrutinib added to R-CHOP in a phase 1 trial of 18 newly diagnosed patients. 100% RR both GCB and non-GCB. Lancet Oncol 15:1019, 2014
- Ibrutinib used in 80 relapsed/refractory patients. 37% RR for ABC, 5% for GCB. Nature Med 21:922, 2015
- Ongoing trial started in 2013: R-CHOP +/- ibrutinib in ABC DLBCL
- Alliance 51301 phase III trial adding ibrutinib to transplant regimen for relapsed patients followed by 12 months of ibrutinib.
Cell surface antigens present on lymphocytes: potential targets for therapy in lymphomas
Monoclonal Ab development: Anti CD-19 and -22 monoclonal antibodies in DLBCL—what took so long?

- Rituximab was approved for use in 1997
- Clinical trials in the 1980’s and 1990’s used mouse-derived monoclonal antibodies against CD 19 and CD 22.
- These trials used poorly conjugated agents and were immunogenic, so results of the initial compounds were poor.
- Subsequent studies showed that anti-CD19 and anti-CD22 MoAbs were rapidly modulated upon binding, making them less effective than anti-CD20 MoAbs. It was predicted that these targets might work best in combination with other MoAbs or as immunoconjugates/immunotoxins, or linked to T-cells
- Anti-CD-19/CD-3 Bi-specific T-cell engager (BiTE) clinical trial in NHL started in 2001 and took over 10 years to enroll patients due to toxicity. Results were reported in 2016 J CO 34(10):1104,2016; Blood 127:1410,2016
- Anti-CD22-calicheamicin in immunotoxin was evaluated in 2004 Blood 103:1807,2004
Selected results of monoclonal antibody trials

- Blinatumomab phase II relapsed/refractory trial in 21 patients: 43% RR, 19% CR. 17% neurologic events. 22% dropout from AE’s. Blood 127:1410, 2016
- Epratuzumab (anti-CD22) + R-CHOP phase II in 107 newly diagnosed patients. 96% RR, 74% CR, 3 yr EFS 70% Blood 118,4053, 2011
- Inotuzumab oxogamicin (anti-CD22 immunotoxin) + Rituxan phase II study in 63 relapsed/lymphoma pts prior to ASMT. 29% RR, 28 had ASMT. 22% liver toxicity. Leuk & Lymph 56:2863, 2015
Brentuximab anti-CD30 MoAb conjugate in CD30 positive DLBCL relapsed/refractory disease

44% ORR
17% CR
4 mo PFS
18 mo PFS if CR
15 pts combo With Rituxan
--no clear inc
In response

Blood 125:1394 2015
Immune therapy in DLBCL
Immune surveillance
checkpoint inhibitor regulation

IHC
PD-L1 expression
B cell lymphomas
Check point inhibition

Figure 1: Checkpoint Inhibition via the PD-1 Pathway Puts the Brakes on the Antitumor Response. While PD-1- or PD-L1-Blooming Antibodies Release the Brakes—(A) The antigen-presenting cell (APC) presents antigen (Ag) to the T cell by interaction with B7.1 and CD28. The result is T-cell activation via up-regulation of the T-cell stimulatory proteins, including INF-γ, Bcl-xL, and IL-2. (B) The tumor can similarly activate T cells by presenting Ag, creating an antitumor immune response. However, tumors and T cells can co-express the PD-1 proteins. Phosphorylation via SHP-2 inhibits the production of stimulatory proteins, resulting in T-cell anergy or “exhaustion,” thereby “braking” the T-cell immune response. (C) The administration of PD-1- or PD-L1-blocking antibodies (Ab) “releases the brake” on the antitumor immune response. IL = interleukin; INF = Interferon; MCH = major histocompatibility complex; PD-1 = programmed death 1; PD-L1 = PD ligand 1; TCR = T-cell receptor.

Anti-PD-1 blocks inhibitory signal, permitting T-cell activation
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Selected results checkpoint inhibitors in DLBCL

- Single agent CTLA4 blockade has had low response rates NEJM 375:143,2016
- Single agent phase 1 trial of nivolumab (PD-1 blockade) of 11 patients 36% RR ASH 2014 abs 291
- The highest expression of PD-L1 appears to be on primary mediastinal B-cell lymphoma, EBV-associated DLBCL, and T-cell-rich B-cell lymphoma
- Not yet clear if there is an association between PD-L1 and response to nivolumab
Chimeric antigen receptor T-Cell therapy: CART
Selected results CART therapy

- Phase 1 trial in 7 patients (ZUMA-1) had RR of 71% with 57% CR that have been durable. Mol Ther: J Am Soc Gene Ther 25:285,2017

- Phase II trial: relapsed refractory lymphoma: 111 enrolled, 101 received the CART product. RR 76%, CR 47%, 3 mo PFS 56%, 29% neurologic events. ASH 2016 abs LBA-6
Antibody coupled T-cell receptor therapy ACTR
Cellular therapy in lymphoma: Drive T cells to the malignant cells: CART and ACTR

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<th>Construct</th>
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<td>CD3 multiple stimulatory or costimulatory domains</td>
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Selected results ACTR therapy

- Too early
- Franciscan/IBMT is participating in serial clinical trials in relapsed refractory B-cell lymphomas
- First 3 patients treated were at Franciscan
- Minimal toxicity to date.
Non-hodgkin lymphoma trials open at Franciscan Indianapolis

- UNUM UT-201501 (ATTCK-20-2) ACTR cellular therapy in patients with CD-20 positive relapsed/refractory B-cell lymphoma
- Incyte CITADEL 202: INC B050465 in relapsed/refractory DLBCL
R-CHOP failure

Primary refractoriness

- Eligible for transplant
  - Salvage regimen: R-DHAP, R-ICE, R-ESHAP
    - followed by autotransplant
    - (and maintenance)

- Not eligible for transplant
  - Too old
  - Not responding to salvage
  - No stem cells at harvest
  - Other severe diseases

Early relapse

In the future:
- New salvage regimens targeting refractoriness
  - followed by autotransplant
  - (and maintenance)

Late relapse

- Salvage regimen: R-DHAP, R-ICE, R-ESHAP
  - followed by maintenance
    - lenalidomide
    - anti-PD-1 antibodies

In the future:
- Salvage regimen:
  - R-DHAP, R-ICE, R-ESHAP
  - followed by maintenance
    - lenalidomide
    - anti-PD-1

ASH 2016 Education Book
CONCLUSIONS

• The **promise** of targeted therapy in DLCBL has not been fulfilled during the last decade

• The **premise** of targeted therapy in DLBCL is being fulfilled
  - We need better understanding of the targets and which populations should be targeted (biomarkers)
  - Research takes time and there are often unexpected hurdles
  - Multiple new strategies are likely going to improve outcomes for our patients during the next 5 years
References

NEJM 328:1002-1008, 1993
JCO 23(22):5027, 2005
Hematology; ASH Ed 2016, p. 367
ASH 2016 Education Book