Molecular Basis of Lymphomas: Focus on Personalized Therapy

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Outline

• Non-Hodgkin lymphomas overview
• Clinical features, outcome
• Genetic and molecular pathways
• Molecularly targeted agents
• Future directions and challenges

Non-Hodgkin Lymphomas

• Diverse group of lymphoid neoplasms
• 4% of all cancers, annual incidence 19.6/100,000
• 7th most common cancer
• Significant cause of morbidity and mortality
• 450,000 new cases worldwide
  – 225,000 deaths worldwide
• 80,000 new cases in U.S.
  – 20,000 deaths in U.S.

Non-Hodgkin Lymphomas

• Varied biological phenotype, clinical course, and prognosis
• Standard tx: anthracycline based chemotx
  – CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)
  – Rituximab (anti-CD20) – major improvement
• Complete response rates of 40-50%
• Relapse common; 30% survival
  • Need for better therapies

Non-Hodgkin Lymphomas

• Diverse histological subtypes
• Molecular heterogeneity, both across and within histological subtypes
• Distinct oncogenic mechanisms
• Advances in molecular profiling
• Next-generation sequencing
• Novel treatment strategies based on targeting specific oncogenic alterations

Diffuse Large B-Cell Lymphoma (DLBCL)

• Aggressive B-cell lymphoma
• Most common form of lymphoma in adults
• Accounts for 30-40% of adult NHL
• Clinical and biological heterogeneity
  – Complex molecular profiles
• Molecular subgroups with unique genetic alterations and discreet oncogenic pathways
  – Therapeutic targets
• Potential for personalized medicine approach
Immunochemotherapy for DLBCL

- R-CHOP - standard of care
  - Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
- Most commonly used therapy for DLBCL
- 5 year progression free survival 50%-65%
- Limited options for patients who fail R-CHOP and most will succumb to their disease
- Significant potential to explore novel therapies

DLBCL Outcome

- Treated with R-CHOP:

DLBCL

- Gene expression profiling (GEP)
- Two molecular subtypes
  - Activated B cell (ABC) - aggressive, worse outcome
  - Germinal center B-cell like (GCB)
- Different stages of lymphoid differentiation
- Unique intracellular oncogenic signaling pathways \(\rightarrow\) prognostic/therapeutic implications
- Select who needs more aggressive therapies

DLBCL subtypes

- Activated B-cell (ABC) – 50%
  - 3y survival 56%
  - Constitutive activation of NF-κB via multiple distinct genetic alterations
- Germinal center B-cell (GCB) – 30%
  - 3y survival 84%
  - Mutations affecting epigenetic modification (EZH2, CREBBP, MLL2)
- Primary mediastinal B-cell lymphoma (PMBL)
Etiologic Factors in Lymphomagenesis

- Aberrant cell-cycle regulation
- Deregulated cytokines
- Loss of normal immune surveillance
- Epigenetic abnormalities

Key oncogenic pathways in DLBCL

Genetic and Molecular Targets in Lymphoma

- NF-κB
- BCL-2 t(14:18)
- JAK-STAT pathway
- PI3K/AKT/mTOR pathway
- C-myc
- B-cell receptor signaling complex
- Immunomodulatory drugs

NF-κB Pathway

- NF-κB family regulates the transcription of proteins mediating cell proliferation and survival in lymphocytes
- High NF-κB expression noted in B and T cell lymphomas
- Constitutive activation of NK-κB pathway in lymphoma
- Important target in lymphoma therapy
**BCL2**

- BCL-2 - important regulator of apoptosis
- Chromosomal translocation t(14:18) in follicular lymphoma → increase BCL2
- High BCL-2 expression confers anti-apoptotic properties and resistance to chemo
- BCL-2 small molecule inhibitors in development

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**JAK-STAT Pathway**

- Janus kinase (JAK) is a signal transducer and activator of transcription (STAT)
- Targeting the JAK-STAT pathway causes cell death in lymphoma
- JAK 2 inhibitors promote apoptosis, inhibit proliferation, decrease inflammatory cytokines
- Phase II study of JAK inhibitor in progress

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**PI3K Pathway**

- Enzymes which phosphorylate/activate many kinases
- Cellular growth, angiogenesis, cell survival
- PI3K/AKT/mTOR
- Combination of mTOR inhibitor (everolimus) and RCHOP
MYC Alterations in Lymphoma

- Transcription factor with strong oncogenic potential
- MYC proto-oncogene family regulate multiple cellular functions: cellular proliferation, DNA replication, metabolism
- MYC and BCL2 (BCL6) rearrangements seen together confer more aggressive clinical course

“Double-hit” Lymphomas

- MYC and BCL-2 translocation
- Very poor outcome with standard R-CHOP
- Resistant to chemotherapy
- 30% of DLBCL express high levels of MYC and BCL2
- Optimal treatment unknown

B-Cell Receptor Signaling

- Critical for B-cell lymphomagenesis
  - Activated B-cell (ABC) DLBCL
- Constitutive activation essential for survival/proliferation of malignant B cells
- Major therapeutic target
- Therapeutic potential of targeting B-cell receptor (BCR) downstream effectors
**B-Cell Receptor Signaling**

- B-cell receptor (BCR) signaling - upstream of key regulatory elements/pathways implicated in ABC DLBCL
- SYK – spleen tyrosine kinase
- BTK – Bruton’s tyrosine kinase
- PKCβ – protein kinase C-β
- IKK- IKB Kinase \(\rightarrow\) upregulation of NK-κB

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**Bruton’s Tyrosine Kinase Inhibitor**

- BTK – tyrosine kinase in BCR signaling cascade
- Ibrutinib – oral, first-in-class, small molecule inhibitor of BTK
- Covalently binds Cys-481 residue in BTK, blocking its enzymatic activity
- Highly toxic to ABC DLBCL
- Promising activity in MCL, CLL, ABC DLBCL

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**BTK Inhibitor: Ibrutinib**

- First drug approved in its class for lymphoma
- Single agent response rates 40-50%
  - Diarrhea, skin reactions
- Combined with R-CHOP – overall response rates of 94% in phase I/II trials
- Phase III trial of R-CHOP +/- Ibrutinib in patients with newly diagnosed non-GCB DLBCL in progress (PHOENIX trial)
Ibrutinib in Waldenström’s

- 63 patients with symptomatic Waldenström’s macroglobulinemia
- Median IgM levels decreased from 3520 mg to 880 mg
- Hgb increased from 10.5 g/dL to 13.8 g/dL
- Overall RR 90.5%
- Highest response in MYD88 mutation carriers

Targeting BTK with Ibrutinib

- 111 patients with relapsed or refractory MCL
  - Median age 68
  - 86% had intermediate/high risk MCL
- Overall response rate 68% (87% w/ Rituximab)
  - Complete response rate 21% (13.9 mos PFS)
  - Partial response 47%
- Side effects: moderate diarrhea, fatigue, nausea

Ibrutinib in Mantle Cell Lymphoma

- Similar excellent response in high risk MCL
  - Blastoid histology or high MIPI score
- Highest response rates for a biologically targeted single agent in relapsed/refractory MCL
- Accelerated FDA approval
- Incorporated into both frontline and second-line treatment paradigms in combination with other therapies

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**Spleen Tyrosine Kinase Inhibitors**

- SYK – tyrosine kinase in BCR signaling cascade
- Fostamatinib – small molecule inhibitor of spleen tyrosine kinase (SYK)
- SYK depletion inhibits proliferation of BCR-dependent DLBCL cell lines
- 24% overall response rate in both indolent and aggressive B-cell NHL (Phase II trial in progress)

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**Proteasome Inhibitors**

- Bortezomib – proteasome inhibitor
- Prevents breakdown of IKKα, resulting in repression of NF-κB
- Induces apoptosis in ABC DLBCL (not active in GCB DLBCL)
- Active in Mantle Cell Lymphoma – ORR 50%
- Enhances cytotoxicity of chemo agents
- Carfilzomib – 2nd generation proteasome inhibitor, more selective

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**Immunomodulatory Agents**

- Lenalidomide – oral immunomodulatory drug
- Inhibits interferon regulatory factor 4 (IRF4)
  - IRF4: transcription factor, increases activity of NFκB
- Lenalidomide indirectly downregulates NFκB
- Lenalidomide + RCHOP - 92% response rate
- Similar efficacy between GCB and non-GCB
PI3K and B cell activation

• Phosphatidylinositol 3-kinase (PI3K)
• Lipid kinase with four isoforms: α, β, δ, γ
  – Y and δ restricted to hematopoietic cells
• Activation of PI3K generates phospholipid second messengers → proliferation, survival
• B lymphocytes: δ isoform (PI3Kδ) plays central role in B-cell function, signal transduction, proliferation

PI3Kδ Inhibitors

• PI3Kδ mediates B-cell receptor signaling
  – Promotes growth and survival of malignant B-lymphocytes
• Idelalisib – potent, orally active PI3Kδ inhibitor
  – Highly selective for δ isoform
  – Blocks PI3Kδ - AKT signaling
• Antitumor activity in refractory indolent NHL

Indolent Non-hodgkin’s Lymphoma

• Comprise one third of all NHL
• Follicular, small lymphocytic, marginal-zone
• 20,000 diagnosed in U.S.; 7,000 people die/yr
• Mainstay of tx: anti-CD20 Ab (rituximab) with chemotherapy (alkylators, anthracyclines)
  – Not curative; multiple toxicities
• Need for new therapy, novel mechanisms

PI3Kδ Inhibition by Idelalisib (NEJM ’14)

• 125 patients w/ indolent NHL
• Resistant/refractory to rituximab, alkylator
  – Median of 4 prior therapies (heavily pretreated)
• Idelalisib 150 mg twice daily
• 57% response rate, 6% complete response
• 12.5 month median duration of response
• Favorable toxicity profile
• Neutropenia 27%, diarrhea 13%

Emerging new molecular targets

• Novel targets and treatment strategies
  – PKC-β - regulator of apoptosis
  – EZH2 - methylation of histone groups
  – BET family of proteins – facilitate expression of BCL2
  – JAK-STAT - signal transduction, activation of transcription
Combination Strategies

- Overlap in pathways of lymphoma proliferation
- Exploit possible synergy between agents
- Cross-talk between pathways
- Overcome resistance to therapy
- Evidence for oncogenic cooperation of the MYC, BCL2, and PI3K signaling pathways
Summary

- Non-Hodgkin lymphomas posses diverse clinical, molecular, and genetic features
- Recent advances in the laboratory allow for a better understanding of complex molecular pathways involved in lymphomagenesis
- Novel agents targeting specific pathways are making it possible to deliver personalized care with greater efficacy, safety and less toxicity