NON-HODGKIN LYMPHOMA: KNOW YOUR SUBTYPE

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WELCOMING REMARKS
Non-Hodgkin Lymphoma: Know Your Subtype

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WELCOMING REMARKS
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Lyneshia Johnson- Woodland
Internet Radio Show Host, Actress and Comedian
NHL Patient since 2020

Seattle Genetics: honoraria/consultation fee
Non-Hodgkin Lymphomas: Know Your Subtype

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What are lymphomas?

- Cancers that arise from lymphocytes.
- Lymphocytes are the B-cells, T-cells, and NK cells of your immune system.
Lymphocytes

Cells of the Immune System

Immune System

Organs of the Immune System
According to the WHO classification of hematologic malignancies, there are over 50 different types of lymphomas. This is due to the variety of cell types that can become a lymphoma.

**FOLLCULAR LYMPHOMA GRADE 1-2**
- Peripheral T cell lymphoma
- Lymphoplasmacytic lymphoma
- Follicular lymphoma grade 3a
- Lymphoplasmacytic lymphoma

**MANTLE CELL LYMPHOMA**

**MARGINAL ZONE LYMPHOMA**
- Marginal zone lymphoma

**DIFFUSE LARGE B CELL LYMPHOMA**
- Diffuse large B cell lymphoma

**ANAPLASTIC LARGE CELL LYMPHOMA**
- Anaplastic large cell lymphoma

**BURKITT'S LYMPHOMA**
- Burkitt's lymphoma

**SMALL LYMPHOCYTIC LYMPHOMA**
- Small lymphocytic lymphoma
Lymphoma Algorithm

Lymphoma

Hodgkin

Non-Hodgkin's
Hodgkin Lymphoma

- Cell of origin: B cell
- Cause: Unknown
- Distribution:
  - Accounts for about 10-15% of all lymphomas in the US.
  - Mainly found in late adolescent / young adults, but a second peak in incidence is seen in people > 55
- Prognosis: Curable in about 80% of the cases.
- Treatment: Chemotherapy with a regimen called ABVD
Lymphoma Algorithm - NHL

Non-Hodgkin's

Indolent / Low grade
- Follicular (grade 1, 2, and 3a).
  - Marginal zone
  - CLL/SLL
  - Lymphoplasmacytic / WM

Intermediate
- DLBCL
- Follicular grade 3b
- Mantle Cell

Aggressive / High grade
- ALCL
- Burkitt's
- Lymphoblastic
- HIV associated
- PTCL

THE GOOD

THE BAD

& THE UGLY
The Good

- Low grade follicular lymphomas (grade 1, 2, 3A)
- Marginal zone lymphomas
- Small lymphocytic lymphoma / CLL
- Lymphoplasmacytic lymphoma / Waldenstrom’s

Why these are good.

- Very slow growing.
- People can live with these for years to decades.
- Some do not require treatment, and they can just be observed.
- “People die with these, not of these.”
Evaluated 1088 patients with low grade follicular lymphoma.

> 60% still alive at 15 years post diagnosis.

The Bad

- Diffuse large B cell lymphoma.
- Grade 3B follicular lymphoma.
- Mantle cell lymphoma ***
Why these are bad.

- Grow quickly
- Fatal without treatment
- Can NOT be observed

Some good news: Can be cured in certain cases.
- Results of 399 patients treated with CHOP vs RCHOP. Overall survival.

> 60% alive at 5 years post treatment.
The Ugly

- Lymphoblastic lymphoma
- Burkitt’s lymphoma
- Most peripheral T cell lymphomas
- Anaplastic large cell lymphoma without ALK mutation
- HIV associated lymphomas
- Primary central nervous system lymphomas.

Why these are ugly.

- Grow extremely quick. Some will double in size within a matter of days.
- Rapidly fatal without treatment.
Even though they are extremely aggressive, some can be cured.

Dunleavy et al. NEJM. 2013.

Evaluated 19 patients with sporadic Burkitt’s lymphoma.
- Knowing your lymphoma type is important for prognosis.

- Knowing your lymphoma type is also important for determining treatment.
Chemotherapy

- Chemicals that kill fast growing cells.

- Mainly work by attacking some part of the cell process necessary for replication and division (i.e., copying and splitting of DNA strands).

- Not specific for any one cell type.

Examples:
- Cyclophosphamide
- Doxorubicin / Daunorubicin
- Vincristine
- Gemcitabine
- Bleomycin
- Etoposide
- Bendamustine
- Etc.
Chemotherapy

- Pros:
  - Very effective at killing cells.
  - Works well on rapidly growing cells.

- Cons:
  - Not specific for cancer cells.
  - Will also kill other good cells in the body such as blood cells, hair cells, etc.

Targeted Therapies

- Monoclonal antibodies
- Antibody drug conjugates
- Small molecule inhibitors
  - Bruton’s Tyrosine Kinase (BTK) inhibitors
  - Phosphatidylinositol 3 kinase (PI3k) inhibitors
  - BCL2 inhibitors
Chemotherapy vs Targeted therapy

Conventional Chemotherapy

Targeted therapy

Rituximab

- Monoclonal antibody against CD 20.
Rituximab

- Only attacks cells that express CD20.
- If your lymphoma does not express CD20, then this treatment will not work.
- **Know your type:**
  - Will not work on T cell lymphomas or Hodgkin lymphomas.
  - Will work on most B cell lymphomas.

Tafasitamab (Monjuvi)

- Monoclonal antibody against a protein called CD19.
- Will only work on cells that express this protein.
- CD19 positive lymphomas:
  - Diffuse large B cell
  - Follicular lymphoma
  - Marginal zone lymphoma
  - Some types of lymphoblastic lymphomas
Antibody Drug Conjugates (ADC)

- Antibodies that have a poison attached to them.
  - Brentuximab vedotin
    - Anti CD30 antibody plus MMAE (poison)
  - Polatuzumab vedotin
    - Anti CD79b plus MMAE
  - Loncastuximab tesirine
    - Anti CD19 antibody plus SG3199 (poison)

ADC: Brentuximab vedotin

- Brentuximab vedotin (SGN-35) ADC
  - mono-methyl auristatin E (MMAE), potent antitumor agent
  - protease-cleavable linker
  - anti-CD30 monoclonal antibody

ADC binds to CD30
ADC-CD30 complex traffics to lysosome
MMAE is released
MMAE disrupts microtubule network
G2/M cell cycle arrest
Apoptosis

NCI bulletin December 2014.
ADCs

- Know your lymphoma type!
  - Brentuximab vedotin
    - *Only works* on lymphomas that have CD30
      - Classical Hodgkin Lymphoma
      - Anaplastic Large Cell Lymphoma
      - Some types of peripheral and cutaneous T cell lymphomas.
  - Polatuzumab vedotin
    - *Only works* on lymphomas that have CD79b
      - These are mainly your mature B cell lymphomas such as DLBCL and follicular lymphoma.

Small Molecule Inhibitors/
B-Cell Receptor Inhibitors
BCR Signaling Pathway

Dr. Susan O'brien. ASH 2011 oral presentation.

B cell receptor (BCR) signaling pathway

- BCR signaling is required for lymphoma expansion and proliferation.
- Plays and intricate role in responding to the surrounding supporting cells (microenvironment).
- The BCR signaling pathway is composed of several different elements including kinases.
- Inhibitors of these kinases block signaling which can disrupt cell proliferation and induce cell death.
Bruton’s Tyrosine Kinase (BTK)

- Primarily expressed in hematopoietic cells.
- Plays a key role in the BCR signaling pathway.
- Thought to also play a role in cell migration.

Ibrutinib

- Selective BTK inhibitor.
Ibrutinib

- Commonly used BTK inhibitor in CLL/SLL and mantle cell lymphoma.
- Works in other low grade B cell lymphomas with a specific mutation called MYD88.
- Also works in some types of DLBCL:
  - Study showed results varied based on subtype of DLBCL.
    - Overall response rate of 22% in all patients with DLBCL.
    - Response rate in a subtype called Activated B cell Type (ABC) was around 40%.

BTK inhibitors

- Other BTKi now available:
  - Acalabrutinib
    - Approved in mantle cell and CLL / SLL.
  - Zanabrutinib
    - Approved for mantle cell, WM, and marginal zone lymphoma.
Immunotherapy Treatments

Chimeric Antigen Receptor T cells

- Also known as CAR T-cell therapy.

- They are T cells obtained from the patient that are genetically modified to recognize a specific protein on the lymphoma cells.

- The T cells are also engineered to be more efficient “killers”.
CAR T cell therapy cont.

T Cell Activation Requires 2 Signals

Antigen Generates Signal 1

CD8 Costimulation Provides Signal 2

Treatment regimen done per the following diagram (DLBCL example):
CAR T cell cont.

- Current FDA approved CAR T cell products in the US:
  - Brexucabtagene Autoleucel (Tecartus)
    - Anti CD19 CAR T cell approved for mantle cell.
  - Axicabtagene Ciloleucel (Yescarta)
    - Anti CD19 CAR T cell
    - Approved for DLBCL and Follicular lymphoma
  - Tisagenlecleucel (Kymriah)
    - Anti CD19 CAR T cell
    - Approved for DLBCL and certain types of lymphoblastic lymphoma / leukemia (ALL)
  - Lisocabtagene maraleucel (Breyanzi)
    - Anti CD19 CAR T cell approved for DLBCL

Summary

- COMMUNICATION is KEY!
- Lymphoma is not just one type of cancer.
- There are over 50 different types of NHL defined in the WHO classification of hematologic malignancies.
- Diffuse large B cell is the most common type of intermediate / aggressive NHL.
- The type of lymphoma is important for prognosis and for guiding treatment.
The Benefits of Discussing Quality of Life Concerns with Your Healthcare Team

No Two People Are the Same

- Our likes and dislikes differ.
Quality of Life Concerns

- In the aggressive diseases, QoL is not so much an issue.
- In the slow growing diseases, QoL becomes more of an issue.
  - Treatment duration
  - Treatment location
  - Transportation issues
  - Cost

"Age is an issue of Mind over Matter. If you don’t mind, it doesn’t matter."
~Mark Twain
• **Ask a question by phone:**
  – Press star (*) then the number 1 on your keypad.

• **Ask a question by web:**
  – Click “Ask a question”
  – Type your question
  – Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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  Monday to Friday, 9 a.m. to 9 p.m. ET
- **Chat live online:** [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)  
  Monday to Friday, 10 a.m. to 7 p.m. ET
- **Email:** [www.LLS.org/ContactUs](http://www.LLS.org/ContactUs)  
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Patient Podcast
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org.

LLS EDUCATION & SUPPORT RESOURCES

Help With Finances
The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: www.LLS.org/Finances

To order free materials: www.LLS.org/Booklets
We have one goal: A world without blood cancers

THANK YOU