NON-HODGKIN LYMPHOMA

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How the Experts Treat Hematologic Malignancies
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Objectives

- Classification of lymphomas
- Presentation
- Work-up and staging
- Serious complications
- Non-Hodgkin's lymphoma focus:
  - Diffuse large B-cell lymphoma
- Review Symptom management with a non-Hodgkin lymphoma patient
Classification of lymphoma

- Malignancies of normal lymphoid cells which reside predominantly in lymphoid tissues (nodes, spleen, marrow)
- WHO classification based on morphology, immunophenotype, cytogenetics and clinical factors
- Non-Hodgkin lymphoma
  - B-cell
    - Precursor
    - Mature
  - T and NK-cell
    - Precursor
    - Mature
- Hodgkin lymphoma
Origins of lymphoma

Jaffe, E. S. et al. Blood 2008;112:4384-4399
Non-Hodgkin Lymphoma (NHL)

- Most common hematologic malignancy
- 72,000 cases/year in the US
- 5th most common cause of cancer deaths
- 2nd fastest growing malignancy in terms of mortality
- 85% are of B-cell origin
## Practical classification of NHL

<table>
<thead>
<tr>
<th></th>
<th>Indolent</th>
<th>Aggressive</th>
<th>Highly aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival untreated</strong></td>
<td>Years</td>
<td>Months</td>
<td>Weeks</td>
</tr>
<tr>
<td><strong>Response to chemotherapy</strong></td>
<td>Not curable</td>
<td>Curable</td>
<td>Curable</td>
</tr>
<tr>
<td><strong>Example</strong></td>
<td>Follicular lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Burkitt lymphoma</td>
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</tbody>
</table>
Indolent lymphomas

- B-cell lymphomas
  - B-cell CLL/SLL
  - lymphoplasmacytic
  - Hairy cell leukemia
  - Follicular (gr 1-2)
  - Marginal zone
    - Nodal
    - Extranodal (MALT)
    - Splenic
  - Mantle cell*
  - Plasma cell myeloma

- T-cell lymphomas
  - T-cell LGL leukemia
  - Mycosis fungoides
Aggressive lymphomas

- Diffuse large B-cell lymphoma
- Follicular lymphoma (grade 3)
- Peripheral T-cell lymphoma
- Anaplastic large cell lymphoma
- NK/T cell lymphoma
Highly aggressive lymphomas

- Burkitt Lymphoma
- Precursor B lymphoblastic lymphoma
- Precursor T lymphoblastic lymphoma
- Adult T-cell lymphoma/leukemia
Presentation

- Lymphadenopathy (2/3)
- B symptoms - fever (>38), drenching night sweats, weight loss > 10% in 6 months
- Extra nodal sites - GI tract, skin, bone
- Rare - kidney, bladder, adrenal, heart, lungs, breast, testes, thyroid
Differential diagnosis of lymphadenopathy

- Medication (dilantin, sulfonamides, penicillin, hydralazine)

- Rheumatologic (Lupus, RA, Still’s disease, Churg-Strauss)

- Other (sarcoid, Kikuchi disease, amyloidosis, chronic granulomatous disease, Castleman’s disease)
Lymphadenopathy

- Characteristics suggestive of lymphoma:
  - Significant size (ie > 1.5x1.5 cm)
  - Persistence for > 4 weeks
  - Progressive increase in size
- Rapid progressive – aggressive lymphoma
- Wax/waning – indolent lymphoma
Biopsy

- Supraclavicular > cervical/axillary > inguinal
- Excisional biopsy when possible
- CT guided core needle
- FNA - inadequate!
- Send for pathology, immunohistochemistry/flow cytometry
Work-up

- CT scans chest/abdomen/pelvis
- PET scan (aggressive NHL)
- Bone marrow biopsy
- CBC/diff
- BUN/creatinine
- LFTs
- Uric acid
- Electrolytes/calcium
- B2 microglobulin (indolent)
- LDH
- SPEP (indolent)
Serious complications

- Cord compression
- Pericardial disease/tamponade
- Hypercalcemia
- SVC/airway compromise
- Hyperviscosity
- Intestinal obstruction
- Ureteral obstruction
- Tumor lysis syndrome
- ITP/AIHA
Staging system

A – asymptomatic; B - fever, night sweats, 10% wt loss
Risk factors

- Personal history of malignancy
- Family history of malignancy
- Prior radiation, chemotherapy, immunotherapy
- Occupational history
- Crohn’s disease
- Celiac disease
- Lupus, Sjogren’s
- Immunodeficiency disorders
- Organ transplantation
- HIV
Infectious associations

• NK/T-cell lymphomas - EBV
• Adult T-cell leukemia/lymphoma - HTLV1
• Marginal zone lymphomas - H pylori, B burgdorferi, C jejuni, Hepatitis C, and others
• Primary effusion lymphoma, LBCL associated with multicentric CD - HHV-8/ KSHV
• Plasmablastic, Burkitt, DLBCL, CHL - EBV (subset of cases)
Diffuse large B-cell lymphoma

- Most common subtype NHL – 25%
- Median age 65
- Male predominance
Diffuse large B-cell lymphoma

1970’s

CHOP

aggressive chemotherapy

2000

CHOP

+ rituximab
Overall Survival in the Treatment Groups

CHOP winner – equal efficacy with lower toxicity

How does rituximab work?

- Punch holes
- Direct killing
- Recruit immune cells
GELA Study

- 399 newly diagnosed patients with DLBCL
- age between 60 and 80
- randomized to:
  - standard dose CHOP X 8
  - standard dose CHOP + rituximab X 8
Rituximab Improves Survival

**Overall Survival**

Diffuse large B-cell lymphoma- ongoing studies

Many other trials evaluating R-CHOP or R-EPOCH plus a biologic agent!
### International Prognostic Index

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<thead>
<tr>
<th>Pre-Rituxan Era</th>
<th>Rituxan Era</th>
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<tbody>
<tr>
<td>Risk factors</td>
<td>5 yr OS</td>
</tr>
<tr>
<td>0-1</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>42%</td>
</tr>
<tr>
<td>4-5</td>
<td>26%</td>
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Risk factors: age > 60, stage III/IV, >1 EN site, PS, LDH
Treatment of Relapsed DLBCL

- Standard of care is second-line combination chemotherapy followed by autotransplantation in chemosensitive patients
  - 2nd line regimens (R-ICE, R-ESHAP, R-DHAP)

- Stem cell transplantation – how does it work?
  - Auto = Mega-chemo (e.g. BEAM, CBV)
    - Stem cells are to mitigate toxicities
  - Allo = New immune system
Treatment of Relapsed DLBCL

• In the on deck circle
  – CAR T-cells
  – PD-1/PD-L1 inhibitors (e.g. nivolumab)
  – Bispecific antibodies (e.g. blinatumomab)
  – Antibody drug conjugates (e.g. polatuzumab vedotin)
  – Small molecules/kinase inhibitors (e.g. ibrutinib)
Non-Hodgkin's lymphoma:

- Often presents with lymphadenopathy but any organ may be involved
- Excisional or core biopsy to determine subtype
- Staging with CT +/- PET and bone marrow biopsy
- Aggressive lymphoma is curable in > half of patients with combination chemotherapy
- Indolent lymphoma is not curable with standard chemotherapy, but patients may have long remissions and survival
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Rituximab

- Premedications
  - Tylenol 650 mg
  - Benadryl 50 mg IV
  - Hydrocortisone 100mg IV
  - Others: Ativan, Pepcid

- 1st Infusion: Titrating rates starting at 50 mg/hr, titrate at 50 mg/hour every 30 minutes, maximum of 400mg/hr.

- Subsequent infusions: Titrating rates starting at 100 mg/hr, titrate at 100 mg/hour every 30 minutes in the absence of infusion toxicity, maximum of 400mg/hr.
Rituximab Hypersensitivity Reactions

- Urticaria (hives)
- Hypotension
- Rigors/Chills
- Angioedema (tightening of throat, swelling, etc…)
- Nausea
- Back pain
- Pruritis
- Shortness of breath
- Fever
- Myocardial infarction
- ARDS (Acute respiratory distress syndrome)
- V-Fib
- Death
Treatment for Hypersensitivity Reactions

- Stop infusion
- Vitals, pulse oximetry
- Oxygen
- IV Demerol (for rigors)
- Repeat premedications
- Restart when symptoms resolve
Common R-CHOP/R-ICE Side Effects & Management

- Immunosuppression (time, Neupogen®, Neulasta®)
- Fatigue (exercise)
- Thrombocytopenia (time, platelet transfusions)
- Infection (antibiotics, IVIG)
- Hair loss (time, wigs)
- Mucositis (Magic Mix, good oral hygiene)
- Neuropathy (gabapentin, amitriptyline, Lyrica®)
- Abdominal pain (antacids, stool softeners, laxatives)
- Nausea (antiemetics, distraction, non-greasy foods, etc…)
- Insomnia (sleep agents e.g. Ambien®, Restoril®, trazodone etc…)
Autologous Stem Cell Transplant

- Stem cell transplants are used to treat lymphoma patients who are in remission or relapse during or after treatment.
- Stem cell transplants allow the use of higher doses of chemotherapy and radiation to eradicate disease than would normally be tolerated.
- The high dose conditioning regimen eradicate cancer cells but also destroy the bone marrow, which prevents new blood cells from being formed. This would be fatal if stem cells weren’t given to replace the destroyed bone marrow (stem cell rescue).
- The hematopoietic stem cells used for transplant most often come from the peripheral blood and are mobilized by chemotherapy (Cytoxan/Etoposide are most common), Neupogen® & Mozibil®.
- Stem cells are collected in the blood donor room using an apheresis machine, over the course of one to five days.
Side Effects Post Autologous Stem Cell Transplant

- Very similar to those with R-CHOP and R-ICE regimens but more severe
- Bone marrow suppression
- Systemic infections
- Pulmonary infections (Interstitial Pneumonia Syndrome)
- VOD (rare)
- Graft failure (rare)
Long Term Side Effects Post Autologous Stem Cell Transplant

- Secondary cancers
- Infertility
- Change in vision (e.g. cataracts)
- Bone damage (necrosis, osteoporosis)
- Thyroid dysfunction
- Early menopause for women