Lymphoma
Multiple Myeloma

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Disclosures for
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Speakers Bureau
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Agenda
- Classification of lymphoid malignancies
- Presentation
- Work-up and staging
- Serious complications
- Non-Hodgkin’s lymphoma
  - Diffuse large B-cell lymphoma
  - Follicular lymphoma
- Hodgkin lymphoma
  - Therapy
  - Complications of therapy
- Multiple Myeloma

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’s lymphoma
  - B-cell
    - Precursor
    - Mature
  - T and NK-cell
    - Precursor
    - Mature
- Hodgkin lymphoma

WHO Classification - B Cell NHL
- Precursor B cell neoplasm:
  - Pre-cursor B-lymphoblastic leukemia/lymphoma
- Mature B-cell neoplasms:
  - Diffuse large B-cell lymphoma
  - Follicular lymphoma
  - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)
  - Nodal marginal zone lymphoma
  - Splenic marginal zone lymphoma
  - Mantle-cell lymphoma
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - Hairy cell leukemia
- Lymphoplasmacytic lymphoma
- Plasma cell neoplasms
### WHO Classification – T/NK Cell NHL

**Precursor T Cell Neoplasms:**
- Precursor T-lymphoblastic lymphoma/leukemia
- Peripheral T cell and NK cell Neoplasms:
  - Peripheral T cell lymphoma, unspecified
  - Anaplastic large cell lymphoma
  - Angioimmunoblastic T cell lymphoma
  - T-cell prolymphocytic leukemia
  - T-cell large granular lymphocytic leukemia
  - Aggressive NK cell leukemia
  - Adult T cell leukemia/lymphoma
  - Extranodal NK/T cell lymphoma, nasal type
  - Enteropathy-type T cell lymphoma
  - Hepatosplenic T cell lymphoma
  - Mycosis fungoides/Sezary syndrome

### WHO Classification - Hodgkin lymphoma

- Classical Hodgkin lymphoma
  - Nodular sclerosis
  - Lymphocyte-rich
  - Mixed cellularity
  - Lymphocyte depleted
- Nodular lymphocyte-predominant Hodgkin lymphoma

### Non-Hodgkin’s Lymphoma

- Most common hematologic malignancy
- 66,000 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

### Aggressive lymphomas

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

### 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

### Survival untreated

<table>
<thead>
<tr>
<th>Response to chemotherapy</th>
<th>Indolent</th>
<th>Aggressive</th>
<th>Highly aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival untreated</td>
<td>Years</td>
<td>Months</td>
<td>Weeks</td>
</tr>
<tr>
<td>Not curable</td>
<td>Curable</td>
<td>Curable</td>
<td></td>
</tr>
<tr>
<td>Example</td>
<td>Follicular lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Burkitt lymphoma</td>
</tr>
</tbody>
</table>
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
• Send for pathology, immunohistochemistry/flow cytometry
Work-up
- CT scans chest/abdomen/pelvis
- PET scan
- Bone marrow biopsy
- CBC/diff
- BUN/creatinine
- LFT's
- Uric acid
- Electrolytes/calcium
- B2 microglobulin (indolent)
- LDH
- SPEP (CLL/SLL/waldenstrom’s/lymphoplasmacytoid)

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
Therapy for DLBCL

- 1970’s - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- 1980’s – 2nd and 3rd generation regimens (addition of other active agents, modification of doses and schedules) with improved CR rates and survivals in pilot studies
- 1990’s – prospective randomized trials demonstrate 2nd and 3rd generation regimens are no better than CHOP

Monoclonal Antibody for NHL: Rituximab

- Chimeric molecule with a murine antigen binding domain and human constant region
- Binds to CD20+ expressed on malignant B-cells
- Indolent B-cell lymphoma response rate 50%
- Relapsed large cell lymphoma response rate 37%

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

Overall Survival

How does rituximab work?

Recruit immune cells

Direct killing

Punch holes in cell

Overall Survival in the Treatment Groups


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Overall Survival

**International Prognostic Index**

<table>
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<tr>
<th>Risk factors</th>
<th>5 yr OS</th>
</tr>
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<tbody>
<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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</table>

Risk factors: age > 60, stage III/IV, >1 EN site, PS, LDH

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**Follicular lymphoma**

- Second most common NHL (20%)
- Median age at presentation - 60
- Male to Female – 1:1.7

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**Indolent B-cell lymphoma: clinical management**

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>Advanced Low tumor burden</td>
</tr>
<tr>
<td>Advanced High tumor burden</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Field</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>Involved</td>
<td>Observation</td>
</tr>
<tr>
<td>RT</td>
<td>Therapy</td>
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**Indications for therapy**

- Cytopenias secondary to BM infiltration
- Threatened end-organ function
- Symptoms attributable to disease
- Bulk at presentation
- Steady progression during a period of observation >6 months
- Presentation with concurrent histologic transformation
- Massive splenomegaly

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**Observation vs early therapy**

- Prospective randomized and retrospective studies
- No survival disadvantage
- 3 year median progression to treatment
  - Grade 1: 48 months
  - Grade 2: 16.5 months
- Same rate of histological transformation
- Is an active process, requires periodic monitoring
- Spontaneous remissions can occur

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**Indolent B-Cell lymphoma survival by era**

- 1987-1996 (N=668)
- 1976-1987 (N=513)
- 1960-1976 (N=195)
### Therapy

- Not curable with conventional therapy
- Rituximab + chemotherapy:
  - Bendamustine
  - CHOP
  - CVP
- Maintenance
- Novel agents
- Radioimmunotherapy
- Stem cell transplants may be curative in subset of patients

### Epidemiology

- 9000 cases and 1500 deaths per year in US
- Bi-modal age distribution
  - 20-30’s
  - > 50’s
- Increased incidence in industrialized countries
- NS subtype associated with high standard of living
- MC/LD in economically disadvantaged countries (EBV associated)

### Clinical presentation

- Fever including classic Pel-Ebstein
- Drenching night sweats (25%)
- Pruritus (10-15%)
- Abdominal/groin pain from retroperitoneal disease
- Alcohol induced pain
- Rarely jaundice
- Adenopathy – neck/mediastinum most common

### Hodgkin lymphoma

- Stage I and II Disease
  - Combined modality therapy with chemotherapy and radiation
  - Role for chemotherapy alone
  - Approximately 85%-90% cured with initial chemotherapy

- Stage III and IV Disease
  - Chemotherapy always required
  - Role of radiation therapy to sites of bulky disease uncertain
  - 75% cured with initial therapy depending on risk

### Chemotherapy in HL

- MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) introduced in 1964 at the NCI
  - Late toxicities of MOPP including infertility and myelodysplastic syndrome/AML
- ABVD developed (adriamycin, bleomycin, vinblastine, dacarbazine)
- Intensive regimens – BEACOPP (bleomycin, etoposide, adriamycin, cytoxan, vincristine, procarbazine, prednisone)
On-going research in early HL

- Early stage disease:
  - Given excellent prognosis, focus on preventing long-term complications
  - Less chemotherapy
  - Less radiation
  - Chemotherapy only
- Advanced stage disease:
  - Intensified regimens for patients with poor prognosis
  - Risk adapted therapy using PET scans

HL complications of therapy

- Fertility
  - ABVD low risk of infertility
  - BEACOPP high risk
- Pulmonary Toxicity
  - Bleomycin
- Mediastinal RT
- Cardiac toxicity
  - Mediastinal RT – pericardial, valvular and CAD
  - Doxorubicin - cardiomyopathy
- Second malignancies
  - solid tumors from radiation - breast, lung, etc
  - leukemia with BEACOPP

Multiple Myeloma

- 20,000 new cases per year
- High incidence in African Americans, Pacific Islanders
- Mean age 66
- Etiology: MGUS, irradiation, exposures
- Median survival 5-7 years

Brentuximab Vedotin

- ORR 75% (34% CR) with 96% disease control in relapsed HL
- Monomethyl auristatin E (MMAE), microtubule-disrupting agent
- Protease-cleavable linker
- Anti-CD30 monoclonal antibody
- ADC binds to CD30
- ADC-CD30 complex is internalized and traffics to lysosome
- MMAE is released
- MMAE disrupts microtubule network
- G2/M cell cycle arrest
- Apoptosis
Criteria for Diagnosis of MM
- Monoclonal plasma cells in bone marrow and/or presence of biopsy-proven plasmacytoma
- Myeloma-related organ dysfunction (1 or more)
  - Serum calcium >10.5 mg/dL or ULN
  - Renal insufficiency (SCR >2 mg/dL)
  - Anemia (hemoglobin <10 g/dL or 2g <normal)
  - Lytic bone lesions or osteoporosis

Initial diagnostic evaluation
- Blood:
  - CBC with diff and platelet counts
  - BUN, SCr
  - Electrolytes, calcium, albumin
  - Quantitative immunoglobulins
  - Serum protein electrophoresis (SPEP) and immunofixation
  - β2-microglobulin
  - Serum free light chain
- Urine:
  - 24-hr protein electrophoresis (UPEP) and immunofixation
- Other:
  - Skeletal survey
  - Unilateral bone marrow aspirate and biopsy with cytogenetics

International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival</th>
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| I     | Serum β2M <3.5 g/dL  
       | Serum albumin ≥3.5 g/dL    | 62 mo          |
| II    | Serum β2M <3.5 g/dL  
       | Serum albumin <3.5 g/dL    | 44 mo          |
|       | OR        | Serum β2M 3.5 to 5.5 mg/dL* |             |
| III   | Serum β2M ≥5.5 g/dL | 29 mo          |

Complications
- Bone disease/hypercalcemia
- Hyperviscosity-IgM, IgG3, IgA
- Recurrent infections
- Renal failure: hypercalcemia, myeloma kidney, hyperuricemia, IV urography, dehydration, plasma cell infiltration, pyelonephritis, amyloidosis
- Cardiac failure: amyloid, hyperviscosity, anemia
- Anemia: BM tumors, renal dysfunction, myelosuppression, low endogenous erythropoietin
- Neuropathy: sensory ± motor, amyloid, anti-myelin Ab

MM initial therapy
- Non-transplant:
  - Dexamethasone +
    - bortezomib
    - Lenalidomide
  - Melphalan + Predisone+
    - bortezomib
    - Lenalidomide
    - thalidomide
- Transplant:
  - Two or three drug combinations*:
    - Dexamethasone +
    - Bortezomib
    - Lenalidomide
  - Add cyclophosphamide or doxorubicin in selected cases

Stem cell transplantation
- Autologous transplant:
  - Survival benefit compared with standard therapy
  - Double ASCT:
    - May be of benefit in patients not achieving complete response after 1st ASCT
  - Maintenance with lenalidomide improves outcome but increased secondary malignancies
  - Myeloablative allo-transplant rarely performed due to treatment related mortality

Bisphosphonates for bony disease
Summary

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

Hodgkin lymphoma:
– Often presents in neck and mediastinum
– High cure rates
– Early stage disease treated with combined modality therapy, advanced disease treated with chemotherapy
– Significant long term toxicities of therapy
– Presents with anemia, renal failure, bone dz
– Treatment options: dexamethasone, lenalidomide, bortezomib, thalidomide, melphalan/prednisone, SCT

Question #1
26 year old college student presents with cough, night sweats and 20 lb weight loss. On exam she has bilateral cervical and left supraclavicular lymphadenopathy. Chest CT scan confirms a 4 cm left supraclavicular node and a large mediastinal mass.
The most likely diagnosis is:
- a. Follicular lymphoma
- b. T-cell LGL
- c. Hodgkin lymphoma
- d. Small lymphocytic lymphoma
- e. Burkitt’s lymphoma

Question #2
Which of the following are indications for therapy in the indolent lymphomas?
- a. thrombocytopenia
- b. bulky lymphadenopathy
- c. weight loss
- d. transformation to diffuse large B-cell lymphoma
- e. all of the above
References


- NCCN Clinical Practice Guidelines in Oncology. www.nccn.org


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