Lymphoma: An Overview

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05/03/2103
Overview

• Concepts, classification, biology
• Epidemiology
• Clinical presentation
• Diagnosis/Staging
• Treatment/Prognosis
• Stem cell transplantation
What is Lymphoma?

- Neoplasms of lymphoid origin, characterized by the abnormal proliferation of B or T cells in lymphoid tissue – typically causing lymphadenopathy

- Clonal expansions of cells at certain developmental stages
Hematopoietic stem cell

ALL

Lymphoid progenitor

CLL

Lymphomas

naïve

B-lymphocytes

germinal center

T-lymphocytes

MM

Plasma cells

AML

Myeloid progenitor

Myeloproliferative disorders

Neutrophils

Eosinophils

Basophils

Monocytes

Platelets

Red cells
B-cell development

Bone marrow

Lymphoid tissue

stem cell

lymphoid progenitor

progenitor-B

pre-B

immature B-cell

mature naïve B-cell

germinal center B-cell

memory B-cell

plasma cell

ALL

DLBCL, FL, HL

MM

CLL

B-cell development
Mechanisms of lymphomagenesis

• Genetic alterations
• Infection
• Antigen stimulation
• Immunosuppression
Epidemiology

- $5^{th}$ most frequently diagnosed cancer in both sexes
- Males > females
- Incidence
  - NHL increasing
  - HL decreasing
Diagnosis requires an adequate biopsy

- Diagnosis should be biopsy-proven before treatment is initiated
- Need enough tissue to assess cells and architecture
  - open bx vs core needle bx vs FNA
Staging of lymphoma

A: absence of B symptoms
B: fever, night sweats, weight loss
Classification of lymphoma

lymphoma

Hodgkin’s lymphoma
  HL

Non hodgkin’s lymphoma
  NHL
Relative frequencies of different lymphomas

Non-Hodgkin Lymphomas
- Diffuse large B-cell
- Follicular
- Other NHL

~85% of NHL are B-lineage
Three common lymphomas

- Follicular lymphoma (NHL)
- Diffuse large B-cell lymphoma (NHL)
- Hodgkin lymphoma (HL)
Non Hodgkin’s Lymphoma (NHL)

- Most common hematologic malignancy
- 60,000 new cases annually
- 6th leading cause of cancer death
- Incidence rising
  - overall incidence up by 73% since 1973
  - “epidemic”
  - 2nd most rapidly rising malignancy
NHL

- Lymphoma without of Reed-Sternberg cell
- B lymphocyte more than T lymphocyte
- Identification of CD’s (cluster determinants)
  - CD5 = T cell type
  - CD20 = B cell type
- Extranodal involvement is common, more than HL
Risk factors for NHL

- Immunosuppression or immunodeficiency
- Connective tissue disease
- Family history of lymphoma
- Infectious agents
- Ionizing radiation
Clinical manifestations

• Variable
  • severity: asymptomatic to extremely ill
  • time course: evolution over weeks, months, or years

• Systemic manifestations
  • fever, night sweats, weight loss, anorexia, pruritis

• Local manifestations
  • lymphadenopathy, splenomegaly most common
  • any tissue potentially can be infiltrated
Biology

• Indolent vs. Aggressive NHL
  – key principle in understanding biology, & approach to the patient
  – Indolent = incurable
  – Aggressive = curable

• Chromosomal Abnormalities in NHL
  – frequent chromosomal translocations into Ig gene loci
    • t(8;14), t(2;8), t(8;22) Burkitt’s
    • t(14;18) follicular NHL
• Aggressive NHL
  – short natural history
  – disease of rapid cellular proliferation

• Indolent NHL
  – long natural history
  – disease of slow cellular accumulation
Indolent NHL

- Small cell lymphocytic
- Follicular
- Mantle cell
- Splenic marginal zone lymphoma
- MALT lymphoma
- Lymphoplasmacytic NHL
Aggressive NHL

- Diffuse large B cell
- Diffuse mixed cell lymphoma
- Burkitt's lymphoma
- Anaplastic large cell lymphoma
- Diffuse mixed cell lymphoma
NHL: Classification

• Key Points
  – cell size: small cell vs. large cell
  – nodal architecture: follicular vs. diffuse

• Principle
  – More aggressive: diffuse, large cell
  – More indolent: follicular, small cell
NHL: Approach to the Patient

• Approach dictated mainly by histology
  – reliable pathology crucial

• Approach also influenced by:
  – stage
  – prognostic factors
  – co-morbidities
Staging evaluation

• History and PE
• Routine blood work
  • CBC, diff, plts, electrolytes, LFT’s, uric acid, LDH, B2M
• Lymph node excision biopsy, image guided needle biopsy
• CT scans chest/abd/pelvis
• Bone marrow evaluation
• Other studies as indicated (lumbar puncture, etc...)}
Prognosis

• Poor prognostic signs
  – Increased age
  – Advanced stage
  – Concomitant disease
  – Raised LDH
  – T cell lymphoma

• 5-years survival for treated patients
  – > 50% low grade
  – 30% high grade
Indolent NHL: typical scenario

• patient presents with painless adenopathy
• otherwise asymptomatic
• follicular small cell histology
• average age 59
• usually stage III-IV at diagnosis
Follicular Lymphoma

- Most common type of “indolent” lymphoma
- Usually widespread at presentation
- Often asymptomatic
- Incurable (some exceptions)
- Associated with BCL-2 gene rearrangement[t(14;18)]
- Cell of origin: germinal center B-cell
• Indolent NHL: guiding treatment principle
  – early treatment does not prolong overall survival

• When to treat?
  • constitutional symptoms
  • compromise of a vital organ by compression or infiltration, particularly the bone marrow
  • bulky adenopathy
  • rapid progression
  • evidence of transformation
Indolent NHL: typical scenario

- Watchful waiting: 2-4 years
- First remission length: 3-4 years
- Second remission: 2-3 years
- Third remission: 1-2 years
- Each subsequent remission shorter than prior
- Median survival 8-12 years for FLSC
Indolent NHL: treatment options

- watchful waiting
- radiation to involved fields
- single agent chemotherapy
  - chlorambucil + prednisone, fludarabine
- combination chemotherapy
  - CVP, CF, FND, CHOP
- chemotherapy + interferon
- chemotherapy + monoclonal antibodies
- monoclonal antibodies
- radiolabeled monoclonal antibodies
- stem cell transplantation
Aggressive NHL: typical scenario

• Patients notes B symptoms of several weeks duration
• Work-up reveals pathologic adenopathy
• Histology: diffuse large cell lymphoma
• ~ 50% patients stage I-II, 50% stage III-IV
• Average age 64
• IPI score
Diffuse large B-cell lymphoma

- Most common type of “aggressive” lymphoma
- Accounts for ~ 31% of all lymphomas
- Usually symptomatic
- Extranodal involvement is common
- Cell of origin: germinal center B-cell
- Treatment should be offered
- Curable if chemo-sensitive upfront, not so if chemo-refractory or relapses within 6 months
Aggressive NHL: treatment approach

- Stage I-II: combined modality therapy
  - CHOP chemotherapy x 3 + IF radiotherapy
  - cure rate around 70%
- Stage III-IV (also bulky stage II)
  - (R)CHOP chemotherapy x 6-8 cycles
  - cure rate around 40%
- (R)CHOP is the standard
Other complications of lymphoma

- Bone marrow failure (infiltration)
- CNS infiltration
- Immune haemolysis or thrombocytopenia
- Compression of structures (eg spinal cord, ureters)
- Pleural/pericardial effusions, ascites
• International Prognostic Index
  – Risk Factors (0-5)
    • age > 60
    • two or more extranodal sites
    • performance status ≥ 2
    • elevated LDH
    • stage III-IV
  – Age adjusted IPI (0-3)
### CR and OS stratified by IPI

<table>
<thead>
<tr>
<th># RF’s</th>
<th>CR</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0,1</td>
<td>87%</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>67%</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>55%</td>
<td>43%</td>
</tr>
<tr>
<td>4,5</td>
<td>44%</td>
<td>26%</td>
</tr>
</tbody>
</table>
Role for Autologous Stem Cell Transplantation

• Aggressive NHL
  – clear benefit when used for aggressive NHL in first relapse in appropriately selected patients
  – 1/3 of these patients can be cured by SCT

• Indolent NHL
  – no indication that patients are cured
  – no indication that OS is prolonged
NHL: future directions

• Indolent
  – monoclonal antibodies (Rituximab)
  – radiolabeled monoclonal antibodies
  – chemotherapy combined with antibodies
  – antibodies combined with immunomodulators

• Aggressive
  – risk stratification
  – CHOP vs. CHOP plus SCT
  – chemotherapy plus antibodies

• Clinical Trials
Treatment

**grade**

- **Low grade**
  - Without symptoms: Watchful waiting
  - With symptoms: Localizes
    - Radiotherapy

- **High grade**
  - Chemotherapy (CHOP), biological therapy & Radiotherapy

- **Relapse disease**
  - High dose of chemotherapy & stem cell transplanted
Hodgkin lymphoma

- Cell of origin: germinal centre B-cell
- Reed-Sternberg cells (or RS variants) in the affected tissues
- Most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells
Reed-Sternberg cell

binucleate Hodgkin cell with owl eye appearance
RS cell and variants

- classic RS cell (mixed cellularity)
- lacunar cell (nodular sclerosis)
- popcorn cell (lymphocyte predominance)
A possible model of pathogenesis

- transforming event(s)
- germinal centre B cell
- EBV?
- RS cell
- loss of apoptosis
- cytokines
- inflammatory response
Hodgkin lymphoma
Histologic subtypes

• Classical Hodgkin lymphoma
  – nodular sclerosis (most common subtype)
  – mixed cellularity
  – lymphocyte-rich
  – lymphocyte depleted
Epidemiology

• Less frequent than non-Hodgkin lymphoma
  • 14% of malignant lymphomas

• Overall M>F

• Bimodal age distribution
  – First peak in 20s /30s
  – Second peak > age 50

Mixed cellularity (MC) Hodgkin’s Disease is more common at younger ages
Associated (etiological?) factors

Pathogenesis of HD is still largely unknown

- EBV infection
- Higher socio-economic status
- Caucasian > non-caucasian
- Possible genetic predisposition
- Other: HIV? occupation? herbicides?
Clinical Presentation

- Nontender lymph nodes enlargement (localized)
  - neck and supraclavicular area
  - mediastinal adenopathy
  - other (abdominal, extranodal disease)
  - Contiguous spread
  - Extranodal sites relatively uncommon except in advanced disease

- Systemic symptoms (B symptoms)
  - fever
  - night sweats
  - unexplained weight loss (10% per 6 months)

- other symptoms
  - fatigue, weakness, pruritus
  - cough, chest pain, shortness of breath, vena cava syndrome
  - abdominal pain, bowel disturbances, ascites
  - bone pain
## HL Clinical Presentation

<table>
<thead>
<tr>
<th>SIGNS &amp; SYMPTOMS</th>
<th>% OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>90</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>60</td>
</tr>
<tr>
<td>“B” symptoms</td>
<td>30</td>
</tr>
<tr>
<td>Fever, weight loss, night sweats</td>
<td></td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>25</td>
</tr>
</tbody>
</table>

- Most commonly involved lymph nodes are the cervical and supraclavicular in 75%
- Bone marrow is involved in 5% of patients
Interesting Features

• Pel Ebstein fevers
• Alcohol-induced pain
Staging Evaluation

- H & P
- CBC, diff, plts
- ESR, LDH, albumin, LFT’s, Cr
- Lymph node excision biopsy, image guided needle biopsy
- CT scans chest/abd/pelvis
- bone marrow evaluation
- **PET or gallium scan**
- **lymphangiogram or laparotomy**
Modified Ann Arbor Staging

• “E” designation for extranodal disease
• B symptoms
  • recurrent drenching night sweats during previous month
  • unexplained, persistent, or recurrent fever with temps above 38 C during the previous month
  • unexplained weight loss of more than 10% of the body weight during the previous 6 months
• Criteria for bulk
  – 10 cm nodal mass
  – mediastinal mass > 1/3 thorax diameter
• Adverse prognostic features for stage I & II (EORTC data)
  • more than 3 nodal sites
  • bulky adenopathy
  • ESR > 50
  • B symptoms
  • invasion into critical organs
  • male
  • age > 40
  • MC or LD subtype

  – should probably not receive XRT alone if any of the above present (excessive relapse rate)
Independent adverse prognostic factors

- Advanced stage (III-IV)
- Male sex
- Age > 45
- Albumin < 4 gm/dl
- HgB < 10.5 mg/dl
- Stage IV disease
- WBC count > 15,000/mm³
- Lymphocyte count < 600/mm³

(Hasenclever et al, NEJM 339,1506-1514;1998)
Treatment

• With appropriate treatment about 85% of patients with Hodgkin’s disease are curable
• Approach depends upon stage, prognostic factors, and co-morbidities
• Stage I-II
  • consider XRT, chemotherapy, or combined therapy
• Bulky stage I-II
  • combined modality therapy
• Stage III-IV
  • ABVD x 6-8 cycles gold standard
# Treatment and Prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Failure-free survival</th>
<th>Overall 5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I,II</td>
<td>ABVD x 4 &amp; radiation</td>
<td>70-80%</td>
<td>80-90%</td>
</tr>
<tr>
<td>III,IV</td>
<td>ABVD x 6</td>
<td>60-70%</td>
<td>70-80%</td>
</tr>
</tbody>
</table>
Hodgkin’s Disease

• Results of Treatment

<table>
<thead>
<tr>
<th>stage</th>
<th>5 year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>90%</td>
</tr>
<tr>
<td>III</td>
<td>80%</td>
</tr>
<tr>
<td>IV</td>
<td>65%</td>
</tr>
</tbody>
</table>
Hodgkin Lymphoma

- Late Complications
  - depends upon treatment modality utilized
  - XRT vs. MOPP vs. ABVD vs. CMT
  - issues depends upon the age of patient
    - relative risks higher in younger patients
    - absolute risks higher in older patients
  - major focus of current clinical trials to maintain high cure rate while minimizing late complication
    - shorter courses of chemotherapy with lower radiation doses in smaller fields
    - elimination of radiotherapy
Long term complications of treatment

- Infertility
  - MOPP > ABVD; males > females
  - sperm banking should be discussed
  - premature menopause
- Secondary malignancy
  - skin, AML, lung, MDS, NHL, thyroid, breast...
- Cardiac disease
Role for Stem Cell Transplantation

- Clinical trials show benefit for patients who receive high dose chemotherapy followed by SCT for patients who
  - Relapse after initial therapy
  - Are primary refractory
# HODGKIN’S DISEASE/LYMPHOMA SALVAGE REGIMENS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients</th>
<th>CR/PR</th>
<th>to ASCT</th>
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</thead>
<tbody>
<tr>
<td>DHAP</td>
<td>102</td>
<td>87%</td>
<td>60%</td>
</tr>
<tr>
<td>(dexamethasone, ara-C, cisplatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-BEAM</td>
<td>89</td>
<td>77%</td>
<td>82%</td>
</tr>
<tr>
<td>(BCNU, etoposide, ara-C, melphalan; 2 series)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexa-BEAM</td>
<td>225</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>(above plus dexamethasone; 3 series)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDP</td>
<td>34</td>
<td>62%</td>
<td>88%</td>
</tr>
<tr>
<td>(gemcitabine, dexamethasone, oxaloplatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICE</td>
<td>65</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>(ifosfamide, carboplatin, etoposide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GND</td>
<td>38</td>
<td>64%</td>
<td>--</td>
</tr>
<tr>
<td>(gemcitabine, vinorelbine, liposomal doxorubicin)</td>
<td></td>
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</tbody>
</table>
Complications of stem cell transplantation

- Infection
- Veno-occlusive disease
- Mucositis
- Graft-versus-host disease (GVHD)
General prognosis of stem cell transplantation

- Widely dependent upon disease type, stage, stem cell source
Summary

- NHL incidence increasing, HL decreasing
- HL cure rate quite high
  - approach is dictated mainly by disease stage
- NHL cure rate mediocre
  - approach is dictated mainly by histologic subtype
  - indolent vs. aggressive
    - indolent: watchful waiting perfectly acceptable for asymptomatic patients
    - aggressive: require aggressive treatment ASAP to achieve cure
Approach to the Patient

- HL
  - approach dictated mainly by where the disease is located rather (results of staging) than the exact histologic subtype

- NHL
  - approach is dictated mainly by the histologic subtype rather than the results of staging

Think of long-term complications