LYMPHOMA
Non-Hodgkin’s Lymphoma

- About 71,380 people living in the United States will be diagnosed with lymphoma in 2007. This figure includes approximately 8,190 new cases of Hodgkin lymphoma (4,470 males and 3,720 females), and 63,190 new cases of non-Hodgkin lymphoma (34,200 males and 28,990 females). Hodgkin lymphoma represents about 11.5% of all lymphomas diagnosed in 2007. 4% of new cases and 3% of cancer related deaths.
- Incidence of lymphoma continues to increase from childhood through the 80’s
- More than 10% increase in incidence every 5 years
- Highest increase in US, Europe, Australia
Incidence of NHL is increasing, especially in the elderly (>60 years).


Lymphoma

- More common in males than females and higher in Caucasian than African American individuals
- Burkitt’s lymphoma is more common in tropical Africa
- Adult T-cell leukemia/lymphoma is more common in Japan and the Caribbean
ETIOLOGY-viral

- EBV, a DNA herpes virus found in Burkitt’s lymphoma
- 95% of African cases.
- Disruption of T cell surveillance.
- HCV-chronic antigenic stimulation
- HHV8-Kaposi’s sarcoma
ETIOLOGY-Immune Disturbances

- AIDS
- Post-transplant
- MTX in RA
- Congenital: Wiskott-Aldrich Syndrome (15% develop diffuse large B-cell lymphoma associated with EBV)
  - eczema, thrombocytopenia and infection
ETIOLOGY-Immune Disturbances

- Klinefelter syndrome: primary hypogonadism
- Ataxia telangiectasia: 10% of children develop diffuse large-B cell lymphoma
- Systemic lupus
- Sjogren syndrome: chronic inflammatory disorder characterized by dry mouth, eyes and other mucous membranes
ETIOLOGY

- Infection: H. pylori: MALT lymphoma
- Chemicals:
  - Dilantin-can induce pseudolymphoma
  - Phenoxyherbicides 2,4-D and organophosphates
  - Benzene
  - Solvents
ETIOLOGY

- Nuclear explosions/reactor accidents
- Patients with HD treated with radiation and chemotherapy
- Hair dyes
Classification of Lymphoma

- **Low Grade**
  - Follicular lymphoma (22 percent of all NHL’s)
  - Small lymphocytic lymphoma (6 percent)
  - Mantle cell lymphoma (6 percent)
  - Marginal zone lymphoma (5 percent)
  - Less than 1 percent each: lymphoplasmacytic lymphoma, mycosis fungoides/Sezary syndrome, splenic marginal zone lymphoma

- **Intermediate**
  - Diffuse large B-cell lymphoma (31 percent of all NHLs)
  - Peripheral T-cell lymphoma (6 percent)
  - Anaplastic large cell lymphoma (2 percent)

- **High Grade**
  - Burkitt’s lymphoma
  - Precursor B- cell leukemia/lymphoma
  - T-cell leukemia/lymphoma
Ann Arbor Staging System

- Stage I  Involvement of single lymph node region or a single extralymphatic organ or site (1E)
- Stage II  Involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of an extralymphatic organ or site (IIE)
- Stage III  Involvement of lymph node regions on both sides of the diaphragm or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
- Stage IV  Diffuse or disseminated involvement of one or more extralymphatic organ with or without associated lymph node involvement

A=asymptomatic
B=fever, sweats, weight loss>10% of body weight
Paradox of NHL

<table>
<thead>
<tr>
<th>Lymphoma Grade</th>
<th>Architecture</th>
<th>Stage at Diagnosis</th>
<th>Untreated Survival</th>
<th>Response to Chemo</th>
<th>Cure with Chemo</th>
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<tbody>
<tr>
<td>Low grade</td>
<td>Follicular or diffuse</td>
<td>III-IV</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>High Grade</td>
<td>Diffuse</td>
<td>I-IV</td>
<td>No 3-6 months</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
IPI

- PATIENTS OF ALL AGES
  - Age $> 60$
  - LDH $> \text{normal}$
  - PS $> 2$
  - Ann Arbor Stage III or IV
  - Extranodal involvement $>1$ site

- PATIENTS $< 60$
  - LDH $> \text{normal}$
  - PS $> 2$
  - Stage III or IV
IPI--5 year survival

- Low risk 73% (IPI score 0-1)
- Low-intermediate 51% (IPI of 2)
- High-intermediate 43% (IPI of 3)
- High 26% (IPI 4 or 5)
FLIPI

- Age >60
- Ann Arbor stage III or IV disease
- Hemoglobin level <12
- Number of involved nodal areas >4
- Elevated LDH

5 and 10 year survival rates

- Low risk (0-1 factors) 91% and 71%
- Intermediate risk (2 factors) 78% and 51%
- High risk (3 or more factors) 52% and 36%
Staging

- Biopsy of lesion
- Thorough history with attention to the presence or absence of B symptoms
- PE with attention to node bearing areas
- Size of liver and spleen
- BW: CBC, LDH, Beta-2 microglobulin, uric acid, alk. Phos, calcium, peripheral blood for flow cytometry, renal function, liver function
- Chest x-ray
- CT of C/A/P, PET scan
- Bone marrow biopsy
Treatment

- **Low grade NHL**: increasing number of Rx options
- Watch and wait may be appropriate for asymptomatic patients
- Chemotherapy: single agent or combination
- Interferon
- Involved field radiation
- Monoclonal antibodies: Rituxan
- Radioactive monoclonal antibody (Zevalin)
- Vaccine therapy
- Autologous, allogeneic transplant
Low grade lymphoma

- CVP: Cytoxan 400 mg/m² orally days 1-5
- Vincristine 1.4 mg/m² IV day 1
- Prednisone 100 mg/m² orally days 1-5
- Repeat every 21 days

- Chlorambucil 16 mg/m²/day x 5 days orally every 4 weeks

- Fludarabine 25 mg/m² x 5 days every 4 weeks
Monoclonal antibodies

- Rituximab (anti-CD20 monoclonal antibody)
- 50% response rate in patients who relapse after chemotherapy (approved indication)
- 60% response rate as upfront Rx
  - elderly patients with co-morbidity
  - patients with low volume, but progressive disease
- Time to response 50 days, duration of response averages one year, can be successfully retreated
Radioimmunotherapy Produces a Crossfire Effect

Naked

Radiolabeled

Radioactive antibodies

- Tositumomab (Bexxar)-Iodine-labeled murine anti-CD20 antibody
- Ibritumomab (Zevalin)-Yttrium-labeled murine anti-CD20 antibody
- Given over one week
- 70-80% response in patients who relapse after chemotherapy
- 60-75% response in patients resistant to Rituximab
- No evidence that this treatment is curative
Ideal Rx for low-grade NHL

- Chemotherapy plus vaccine
- At time of relapse consider CHOP/Rituxan followed by autologous stem cell rescue
- Consider high dose Rx at second relapse—radiation may be given in the form of radioactive antibody
- Allogeneic Tx can be considered after failure or for “bad actors”
Vaccine Rx

- Tumor cells fused with hybridoma-producing cell line to generate tumor specific immunoglobulin
- Patients treated with chemotherapy until CR or near CR
- Patients vaccinated with tumor specific immunoglobulin +/- dendritic cells, GM-CSF to provoke both antibody and cellular response
- No toxicity from vaccine
- Patients who have CR with chemo and mount an immune response seem to remain disease free
CHOP-Rituxan

- Rituxan 375 mg/m² IV
- Cytoxan 750 mg/m² IV day 1
- Doxorubicin 50 mg/m² IV day 1
- Vincristine 1.4 mg/m² IV day 1
- Prednisone 100 mg/m² po days 1-5
Aggressive NHL

- No advantage with second and third generation regimens compared to CHOP (ProMACE-CytaBom and MACOP-B)
- Approximately 40% of patients will be cured with conventional chemotherapy
- Cure rate <50% in patients with 2 or more adverse factors

Combination chemotherapy is the treatment of choice for advanced stage aggressive lymphoma.

- Combination chemotherapy not previously seen by the patient is used to induce a remission in patients with relapsed disease (ICE)
Highly Aggressive Lymphoma

- Burkitt and Burkitt’s like lymphoma
- Hyper CVAD:
  - Fractionated Cytoxan, Vincristine, Adriamycin, Decadron
  - Alternate with Methotrexate and Ara-C
- With CNS prophylaxis
Ovary
T-cell lymphoma

- Tends to be more aggressive
- Often involves the skin
- Skin directed therapies:
  - Chemotherapy with BCNU and Nitrogen mustard
  - PUVA (Psoralen activated in the skin by ultraviolet light)
  - electron beam RT
- Systemic Therapies:
  - Photopheresis: systemic pretreatment with oral or parenteral psoralens, removal of a sample of blood, pheresis of WBCs followed by exposure to UVA. Irradiated cells then reinfused.
  - Combination chemotherapy
Hodgkin’s Disease

- In developed countries: HD has two peaks, one in young adults 20-30. A second peak in people 70-80.

- Etiology:
  - Some familial patterns
  - Woodworking
  - Benzene exposure
  - Exposure to EBV
NHL vs Hodgkin’s Disease

- Hodgkin’s
  - Age-adolescent
  - Spread-contiguous
  - Symptoms-frequently
  - Sweats, weight loss, fever

- NHL
  - Incidence increased with age
  - Spread-erratic
  - Symptoms-infrequent
  - Constitutional symptoms
S/S of Hodgkin’s

- Painless lymphadenopathy
- B symptoms
- Pruritis (can be initial symptom)
- Pain: alcohol induced pain in involved areas
- Hepatosplenomegaly
- Masses: retroperitoneal, mediastinal, hilar
- Bloodwork: lymphocytosis, elevated LDH, elevated ESR, hypercalcemia
Hodgkin’s disease
Classification

- **Lymphocyte predominant (10-15%)** Middle age peak. Males predominate. Usually present with Stage I or II. Outcome favorable. B symptoms uncommon.

- **Nodular sclerosing (30-70%)** Lymph node divided into nodules by sclerosing bands of collagen. Young females. Stage I and II. Age 15-34. A variation of R-S cell (lacunar cell) is seen. Anterior mediastinal involvement is common.

- **Mixed cellularity (20-40%)** Wide age range that peaks in the 30-40 age group. Males more common. More than 50% of patients have Stage III or IV disease. Many have B symptoms.

- **Lymphocyte-depleted (5-15%)** Common in older males. Poor prognosis. Often with B symptoms.
Prognostic Factors-HD

- Early stage, no massive disease, ESR <50, age <50

- Advanced stage, male sex, age >45, Hgb <10.5, albumin <4, stage 4, leukocytosis (WBC >15,000), lymphocytopenia
Dx and Staging-HD

- Removal of complete lymph node
- CT of C/A/P
- PET
- Bone marrow biopsy
- BW: CBC, ESR, LDH, Calcium, uric acid
- Requires presence of at least 1 R-S cell
Early Stage HD (I-IIA)

- Traditionally treated with extended field RT
- 80-85% cure rate
- Avoids acute chemotherapy complications
- Avoids infertility, myelodysplasia/leukemia
- Chemotherapy can salvage most patients who relapse
- Primary RT causes late second cancers in irradiated field, especially breast and lung carcinoma
- RT is associated with increased risk of coronary artery disease
- Chemotherapy plus low dose RT gives higher cure rates and probably less long term complications
Combined modality therapy-HD

- In CMT, radiation doses are lower and limited to the involved field of disease
- Chemotherapy is available that does not cause infertility or MDS/leukemia
- Number of courses of chemotherapy can be reduced because of adjuvant radiation
- Patients generally treated with 4 cycles of chemo followed by 20-30 Gy of RT
MOPP

- First effective chemotherapy (1970)
- 100% male sterility
- age related female infertility
- 5-10% MDS, AML
Advanced HD

- **ABVD** x 12 treatments over 6 months
  - Doxorubicin 25 mg/m² IV days 1 and 15
  - Bleomycin 10 units/m² IV days 1 and 15
  - Vinblastine 6 mg/m² IV days 1 and 15
  - Dacarbazine 375 mg/m² days 1 and 15
  - Cure rate about 60%

- **New Regimens:**
  - Stanford V: finished in 12 weeks and uses less doxorubicin and bleomycin
  - BEACOPP (Europe) most effective regimen yet reported infertility; MDS/leukemia probably similar to MOPP (5-10%)
Recurrent HD

- 2-3 cycles of salvage chemotherapy followed by high dose Rx and autologous stem cell rescue
- 50-70% cure rate
- mortality 1-2% in experienced centers
- MDS/leukemia related to cumulative exposure of chemo prior to high-dose chemotherapy