Hodgkin Lymphoma – Disease Specific Biology and Treatment Options

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My Disclaimer

- This is where I work...
Objectives

- Pathobiology – what makes HL different
- Diagnosis
- Staging
- Treatment Philosophy and Approach
  - Primary Treatment
  - Second-line Therapy
- Summary and Recommendations
- A look forward…
## Hodgkin Lymphoma – Incidence and Prevalence

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<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
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</thead>
<tbody>
<tr>
<td><strong>New HL Cases - Canada</strong></td>
<td>775</td>
<td>436</td>
<td>339</td>
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<td><strong>HL Deaths - Canada</strong></td>
<td>131</td>
<td>72</td>
<td>59</td>
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<td><strong>ESTIMATES FOR EUROPE and NORTH AMERICA</strong></td>
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<td>Incidence -</td>
<td></td>
<td>3 / 100 000</td>
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<td>Prevalence</td>
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<td>350 000</td>
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<tr>
<td>Lifetime Risk</td>
<td></td>
<td>1 / 250</td>
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Current Lymphoma Classification is based on relating disease to normal cell types and development.
Hodgkin Lymphoma - Pathology

- Background of inflammatory cells, eosinophils, fibrosis
- Reed-Sternberg cell is the “malignant cell”
- Immunophenotype shows CD30+ CD15+
- Cell of origin recently shown to be a B lymphocyte

Lazarchick, J. ASH Image Bank 2009;2009:9-00002
Subtypes based on Pathology

- Classical HL
  - Nodular Sclerosis – 55%
  - Mixed Cellularity – 25%
  - Lymphocyte Rich – 5%
  - Lymphocyte Deplete – 1-2%
- Lymphocyte Predominant HL – 5%
Diagnosis – gold standard is biopsy!

- Fine needle aspirate (FNA) – quick, easy no OR but...
- Excisional LN biopsy
  - Lymph node architecture
  - Enough tissue to do additional testing
- Diagnostic sample should be reviewed by expert hematopathologist
Staging – Really simple

- Standard staging includes:
  - A history and physical exam
  - Bloodwork (usually CBC and chemistry tests)
  - CT scans (neck, chest, abdomen, and pelvis)
  - Functional imaging (gallium or PET scan)
  - Bone marrow aspirate and biopsy (if stage III/IV disease or B symptoms)
Staging of Lymphoma – Ann Arbor System

- **A** – absence of any “B” symptoms
- **B** – Unexplained fever, drenching sweats or weight loss
- **Bulky** > 10 cm mass on imaging

Stage I

Stage II

Stage III

Stage IV
Prognostic Score in HL discriminates Overall Survival

Moccia JCO 2012
Decisions regarding Therapy

- Modified for specific instances but *not* individualized yet

- Balance potential toxicity against effectiveness

- Remission ≠ Cure – *why*?
  - Remission is just a state at a specific time
  - Cure is remission maintained forever
Treatment Philosophy in Hodgkin Lymphoma

- Cure!
- In circumstances where cure rate is high
  - ie. localized disease – minimize late effects
- When cure rate is not as high
  - Consider more intensive treatment

IS MORE BETTER?
Chemotherapy

• Works typically through a DNA damaging mechanism – affects all growing cells
  – Lymphoma Cells
  – Blood Cells
  – Lining of GI Tract
  – Hair

• A systemic therapy – treatment travels everywhere through the bloodstream
ABVD – Typical HL Chemotherapy

• ABVD is given every 2 weeks (A and B parts)
  – 1 cycle = 2 treatments and is given over 4 weeks
  – Adriamycin 25 mg/m²
  – Bleomycin 10 u/m²
  – Vinbastine 6 mg/m²
  – Dacarbazine 375 mg/m²
Radiation

- Applies to localized disease
- May not be used in all types of aggressive NHL
- Generally treatment is given daily for 4 weeks (Monday to Friday X 4 weeks = 20 treatments or “fractions”)
- Side effects based on the area that is being radiated (skin and tissue beneath it)
- Doses of radiation are lower than those used in solid cancers
Common Radiation Fields

- Mantle
- Abdominal
- Pelvic
Combined modality Therapy

- Chemotherapy + Radiation = Combined Modality Therapy
- This is our current standard treatment of localized (limited stage) HL
- We do not routinely use radiation as part of the treatment of widespread (advanced stage) HL but may consider for bulky site of disease
Hodgkin Lymphoma

- Cure rate in limited stage disease is 80-95%
- Cure rate in advanced stage disease is 65-80%
- Treatment has evolved over 30-40 years based on application of multiple clinical trials
  - Radiation initially then combination chemotherapy
  - Subsequently more multi-drug regimens (MOPP or MOPP/ABV) and now ABVD
Limited HL – less treatment is just as effective

- 2 cycles of ABVD and lower dose radiation is just as effective as 4 cycles of ABVD and more RT

Engert NEJM 2010
Limited HL – Less toxic treatment is just as effective

• 4 cycles of ABVD and radiation is just as effective as 4 cycles of 7 drug chemotherapy and RT

Engert NEJM 2010
Limited HL – Radiation may help maintain remission

Meyer et al. JCO 2005
Concerns about more intensive regimens in HL

- **Acute toxicities**
  - Low blood counts
  - Higher rates of transfusion and infection

- **Late Toxicity**
  - Infertility
  - Second Cancers

- **Need longer follow-up to accurately understand frequencies of late effects**
  - Other multi-drug regimen studies have NOT shown benefits
Treatment algorithm in Hodgkin Lymphoma

- **Limited stage disease (short course ABVD)**
  - Minimize toxicity
  - Recommend radiation but balance toxicity (second cancer, heart disease) against disease recurrence
    - Smaller radiation field, lower dose
- **Advanced stage disease (longer course ABVD)**
  - Lymphoma recurrence remains an important concern
  - More aggressive chemotherapy?
What happens if primary treatment doesn’t work?

• A minority of patients with HL!
  – Primary refractory disease – lymphoma grows on treatment or within 3 months of completion
  – Relapsed disease – lymphoma grows after 3 months of treatment

• Lymphoma is behaving aggressively – signs that cancer cells have developed drug/radiation resistance
  – But this can be overcome – different drugs and doses
GHSG Transplant Trial – Autologous Transplant improves Outcome in relapsed HL

Schmitz et al. Lancet 2002
Transplant strategies vary center to center

- No studies demonstrate the superiority of one approach over another – variation in:
  - Type of second-line chemotherapy (ICE, GDP)
  - Technique of mobilizing peripheral blood stem cells
  - High dose therapy regimen of the transplant
  - Role of radiation as part of second-line treatment

- Generally, lymphoma needs to respond to second-line chemotherapy for transplant to be successful
A (Canadian) Transplant Strategy

- **Second-line chemotherapy (GDP)**
  - Gemcitabine 1000 mg/² day 1 and 8
  - Dexamethasone 40 mg days 1-4
  - Cisplatin 75 mg/m² day 1

- **Stem Cell Mobilization**
  - Cyclophosphamide 2 g/m² day 1
  - Etoposide 200 mg/m² days 1-3
  - Neupogen 10 ug/kg starting day 6

- **High Dose Chemotherapy**
  - Etoposide 60 mg/kg day -4
  - Melphalan 180 mg/m² day –3
  - Stem Cell Infusion Day 0
PMH Treatment Policy – Limited Stage Hodgkin Lymphoma

• Definition
  – Stage IA (non Bulky)
  – Stage II A (non Bulky)

• Treatment
  – ABVD chemotherapy 2-4 cycles + Involved Field Radiation (30 Gy) depending on amount of disease and some lab parameters
PMH Treatment Policy – Advanced Stage Hodgkin Lymphoma

• Definition
  – Stage III or IV
  – Any Stage with B symptoms
  – Bulky Disease

• Treatment
  – ABVD chemotherapy X 6-8 cycles
  – Radiation if bulky site
PMH Treatment Policy – Relapsed / Refractory Hodgkin Lymphoma

- **ASCT eligible patients**
  - Second-line chemotherapy with GDP
  - Mobilization of stem cells
  - ASCT procedure
  - Consider radiation if bulky disease pre-ASCT

- **Non-ASCT eligible patients**
  - Alternate chemotherapy regimen
  - Radiation
Summary – The Fundamentals of HL

• Confirm the diagnosis

• Accurate Staging

• Treatment is chemotherapy based (ABVD)
  – Remember to think about radiation if the disease is localized

• Second chance of cure with ASCT