Aggressive lymphomas

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What are the aggressive lymphomas?

- Diffuse large B cell
- Mediastinal large B cell
- Anaplastic large cell
- Burkitt lymphoma
- (transformed lymphoma: see next talk)

- T cell lymphomas
lymphoma classification 2012

• Morphology

• Immunohistochemistry

• Cytogenetics

• (gene expression profiling)
Incidence of Follicular Lymphoma: US Cancer Registries 2001

<table>
<thead>
<tr>
<th>WHO histology</th>
<th>Rate/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>7.1</td>
</tr>
<tr>
<td>Follicular</td>
<td>3.2</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>5.2</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>0.5</td>
</tr>
<tr>
<td>Myeloma</td>
<td>5.3</td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>2.7</td>
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*Morton, Blood 2006*
What are the aggressive lymphomas?

• Duration of symptoms generally shorter than indolent lymphomas

• Generally need treatment at time of diagnosis
  – Immediate, few days, few weeks

• Treatment generally given with the expectation of remission, goal of possible cure
**Why pathology is so important in aggressive lymphomas**

- Many/most are potentially cureable—so need to determine the most appropriate therapy
- Some of the criteria for diagnosis are very specific—and lead to specific treatment choices
  - Primary mediastinal lymphoma: use of radiation after chemotherapy
  - CD20 “positive” by immunohistochemistry: use of rituximab
  - T cell lymphoma: type and length of chemotherapy
  - Burkitt lymphoma: specific chromosome change in lymphoma cells, specific chemotherapy treatment programme
Why pathology is so important in aggressive lymphomas

• Specific types of lymphoma may require more or less testing for staging
  – eg lumbar puncture, bone marrow, nuclear medicine tests (Gallium, PET)

• Different subtypes of aggressive lymphoma have variable prognosis—important to know what type you have
Diagnosis starts with a biopsy

- Lymph node biopsies:
- Fine needle aspiration:
  - gives pathologist cells, able to tell lymphoma from other cancer or benign cause.
  - Can provide a lot of information and often the specific type... but is not considered definitive
- Core biopsy, removal of lymph node (excision):
  - Gives pathologist enough tissue to determine arrangement, size of cells, etc... more likely to be definitive
  (but not always)
Lymphomas don’t just arise in lymph nodes

<table>
<thead>
<tr>
<th>Nodal Sites</th>
<th>Extranodal</th>
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<tbody>
<tr>
<td>Neck</td>
<td>GI tract (stomach)</td>
</tr>
<tr>
<td>supraclavicular</td>
<td>bone marrow</td>
</tr>
<tr>
<td>axillary</td>
<td>liver</td>
</tr>
<tr>
<td>groin</td>
<td>skin</td>
</tr>
<tr>
<td>(spleen)</td>
<td>head and neck</td>
</tr>
<tr>
<td>bone</td>
<td></td>
</tr>
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</table>
Staging tests

- CT scans: neck, chest, abdomen, pelvis
  purpose: where is the lymphoma located
  - Needed to determine stage, information re: prognosis, help decide if treatment is working
  - Very important for circumstances where radiation may be considered as part of the treatment plan—generally only if lymphoma is localized to one area
Staging tests for aggressive lymphoma

• Bone marrow biopsy
  Needed for
  – most patients with diffuse large cell lymphoma
  – all patients with T cell lymphoma (bone marrow more likely to be involved)

• Lumbar puncture
  – Some patients where risk of lymphoma in spinal fluid may be higher
  – All patients with symptoms suggesting nervous system involved (Brain MRI would also be done for this concern)
Functional imaging tests: Gallium, PET scan

- Can have role in clarifying if areas of involvement on CT scan represent lymphoma
  - “hot” on scan: likely (but not always)
- Important to determine response if there are still abnormalities on CT at end of treatment
• Staging contributes information about overall prognosis, expected outcomes from treatment
• Along with
  – Performance status: what is the impact of lymphoma (or other medical problems) on daily life – how sick are you?
  – Number of extranodal sites of disease
  – LDH: blood test reflecting amount of lymphoma
  – Age
  
  International prognostic index (IPI)
Treatment of aggressive lymphoma

- CHOP chemotherapy
- Cyclophosphamide
- Doxorubicin
- Vincristine
- Prednisone— pills daily x 5 days

4 cycles—if radiation is also part of the plan
6 cycles—most often
8 cycles—in some circumstances (young people with big masses or other problems)
Why are we so certain that CHOP is the right chemotherapy for aggressive lymphoma?

• Numerous randomized trials of comparing different chemotherapy combinations (>40)
  – CHOP was always as good as other 6-9 drug combinations,
  – less side effects

• Number of cycles (6 v 8) and interval between cycles (2 weeks or 3 weeks) have also been compared: 6 cycles, given every 3 weeks is recommended
  ....at least for B cell lymphomas
Progress in therapy of aggressive NHL subtypes: 1985-present

Comparison of multi-agent chemotherapy regimens: no progress

Addition of anti-CD20 antibody rituximab to chemotherapy: improvement in survival.

targets surface protein which is not prognostic, role in pathophysiology unknown
Impact of Rituximab on Overall Survival of Patients with DLBCL
Age < 60 years

Lee et al. BJH 2012
Impact of Rituximab on Overall Survival of Patients with DLBCL

Age < 61-79 years

Lee et al. BJH 2012
Impact of Rituximab on Overall Survival of Patients with DLBCL

Age >79 years

Lee et al. BJH 2012
Rituximab improves outcome only when CD20 is on cell surface

- Given prior to chemotherapy drugs on each treatment day
- Infusion reactions are common
  - Fever, chills, hives; occasionally shortness of breath, low blood pressure
  - Given very slowly for first few treatments; later treatments given over 90 minutes safely
What to expect on treatment (ie, side effects)

- Hair loss
- Nausea, vomiting: controllable with medication
  - Granisetron, ondansetron; aprepitant
- Fatigue
  - Better with exercise: walking! Exercise bike
- Fever: middle week of the 3 week cycle
  - Need a thermometer! If >38.3 or 101.5 → get a blood test (even Sunday afternoon...)
Other important things

• Heart function: may need monitoring
  – Weakening of heart muscle rare side effect of doxorubicin

• Numb hands, feet: vincristine
  – Not usually disabling but is annoying

• Difficulty with memory, concentration (multi-tasking)—“chemobrain”
  – Improves with exercise
Other important things

• Fertility
  – consequences different for women and men

• Work/school
  – Can I have a normal life? When will my life get back to normal?

• Going out in public, infection risks
  – Not as bad as you think...

• Immunization
  – Get a flu shot
Treatment outcomes

- Variable, depend on many things....
  - Favourable group (IPI score): 90% relapse-free
  - Intermediate prognosis: 60-70%
  - Unfavourable: 40-50% relapse-free

- Long-term remission rates lower for elderly, T cell lymphoma, certain subtypes of B cell (defined by chromosomes, for instance)
What happens if first treatment doesn’t work?

• Difficult question

• For young patients: stem cell transplantation considered best option
  – Autologous stem cells (patients own)
  – Uses very high dose of chemotherapy to try to eliminate resistant lymphoma cells
  – Only beneficial if lymphoma responds to a second chemotherapy regimen
When treatment stops working...

• Many other treatments available, goals of therapy change
  – Single agent chemotherapy drugs
  – Combinations (occasionally)
  – Radiation to local areas causing symptoms

  – Clinical trials of new agents (see next talk)

• Clarification of goals with your oncologist is very important