NON-HODGKIN'S LYMPHOMA

Background

1. Definitions:[1]
    - Non-Hodgkin Lymphoma - cancer which arises from lymphatic system
2. General Information
    - Numerous types based on B-cell or T-cell origin and indolent or aggressive nature[1,2]

Pathophysiology

1. Pathology of Disease[3]
    - Genetic modifications during B-cell development in bone marrow lead to DNA alterations that may become pathologic in lymphomas
2. Incidence, Prevalence[4]
    - Non-Hodgkin's lymphoma
        - Age-adjusted incidence in United States 19.6 / 100,000 for men and women
        - Incidence increasing since 1975, but rate increase slowing since 1991
        - U.S. prevalence ~484,000 cases
3. Risk Factors[5]
    - Single nucleotide polymorphisms (SNPs)
        - TNF-α, IL-10
    - Autoimmune disorders (disease or treatment)
        - Rheumatoid arthritis, celiac disease, systemic lupus erythematosus, Sjogren's syndrome
    - Diabetes mellitus type II
    - Medication use
        - NSAIDs, corticosteroids, immunosuppressants,
        - Possible links: phenytoin, cimetidine, various antibiotics, benzodiazepines
    - Infectious agents
        - HIV, Epstein-Barr virus (EBV), hepatitis-C virus
        - *H. pylori* (MALT lymphomas)
    - Lifestyle
        - *No* correlation to tobacco use
        - *Inverse* correlation to alcohol use
    - Environmental factors
        - Benzene
        - *No* correlation to pesticides, asbestos, occupational/wartime ionizing radiation exposure
4. Morbidity / Mortality
    - Morbidity[6]
        - Treatment-related (radiation and chemotherapy related)
            - Physical functioning

- Appetite loss
- Vitality
- Financial Problems
    - Increased risk of thyroid, lung, breast, other cancers
    - Growth and development retardation
    - Infertility
    - Osteoporosis
    - Cardiotoxicity

- Mortality[5]
    - U.S. age-adjusted death rate 6.6 / 100,000 men and women / year from 2005-09

Diagnostics

1. History[2]
    - Slowly progressive, painless lymphadenopathy
    - "B symptoms"
        - Fever
        - Night sweats
        - Weight loss
2. Physical Examination
    - Painless lymphadenopathy
        - Freely moveable with rubbery consistency
    - Indolent types (follicular, marginal zone and lymphoplasmacytic) present with slowly progressive, painless, peripheral lymphadenopathy
        - Splenomegaly 30-40% of patients
        - Lymphoblastic - anterior mediastinal mass +/- superior vena cava syndrome
    - Aggressive types
        - Extranodal sites in order of frequency
            - GI tract, Skin, Bone Marrow, Sinuses, Thyroid and Central Nervous System
        - American Burkitt's presents with abdominal mass
        - African Burkitt's presents with angle of jaw or neck mass
3. Diagnostic Testing[2]
    - Biopsy
        - Large surgical specimen
        - Excisional lymph node biopsy
            - Fine Needle Aspiration unreliable
        - Bone marrow aspirate/biopsy
    - Immunophenotype
        - CD20, slg increased in all variants
    - Chromosomal testing
        - Most common translocation t(14;18)(q32;q21)
        - Most rearrangements involve *bcl-2, bcl-6,* and *c-myc* genes

4. Laboratory evaluation[2]
    - CBC, electrolyte panel, renal profile, liver profile, LDH
    - β_2-Microglobulin routinely tested in some centers
    - CSF analysis used for patients with:
        - Diffuse large cell NHL with bone marrow involvement
        - High-grade lymphomas
            - Lymphoblastic lymphoma
            - Burkitt lymphoma
            - HIV-related lymphoma
            - CNS lymphoma
        - Epidural masses
        - Testicular involvement
        - Nasopharyngeal involvement
5. Diagnostic imaging[2]
    - CT of neck, chest, abdomen, pelvis
    - PET with fluorodeoxyglucose F 18 (FDG-PET)
        - Used to complement CT for staging and prognostic purposes.
        - Also used to detect relapse
6. Other studies[2]
    - Cerebrospinal fluid evaluation
    - GI evaluation
        - In GI-primary lymphoma and mantle cell lymphoma
7. Diagnostic "Criteria"[2]
    - Lymph node or extranodal tissue biopsy revealing B, T or Natural Killer cell lineage
    - Diagnosis based on abnormal cellular architecture, abnormal immunophenotype, lymphoid cell monoclonality
    - Staging
        - Stage I
            - Involvement of single lymph node region (I)
            - Localized involvement of a single extralymphatic organ or site (IE)
        - Stage II
            - Involvement of two or more lymph node regions on same side of diaphragm (II)
            - Localized involvement of single associated extralymphatic organ or site and regional lymph nodes with or without other lymph node regions on the same side of diaphragm (IIE)
        - Stage III
            - Involvement of lymph node regions on both sides of the diaphragm (III)
            - Involvement of lymph node regions on both sides of the diaphragm + localized involvement of an extralymphatic organ (IIIE)
            - Involvement of lymph node regions on both sides of the diaphragm + splenic involvement (IIIS)

- Involvement of lymph node regions on both sides of the diaphragm + both localized involvement of extralymphatic organ or site and spleen (IIIE-S)
- Stage IV
  - Disseminated involvement of 1 or more extralymphatic organs with or without associated lymph node involvement (IV)
  - Isolated extralymphatic organ involvement + distant (non-regional) nodal involvement (IVE)
- Subclassification (A and B similar to Hodgkin's Lymphoma)

Differential Diagnosis

1. Key Differential Diagnoses
   - Malignancies: Leukemias, Metastases of Unknown Primary
   - Infectious Disease: Cat Scratch Disease, Cytomegalovirus, HIV, Mononucleosis
   - Miscellaneous: Sarcoidosis, Kawasaki's Disease
2. Extensive Differential Diagnoses
   - Medications: Allopurinol, Atenolol, Captopril, Carbamazepine, Hydralazine, Penicillins, Phenytoin, Primidone, Quinidine, Trimethoprim/Sulfamethoxazole, Sulindac
   - Serum Sickness

Therapeutics

- Follicular[8]
  - Stage I and II
    - Radiotherapy (involved or extended field) 30-36 Gy (cure potential)
  - Stage III and IV
    - Induction
      - Spontaneous regression in up to 25% of patients
        - classically, early initiation of therapy did not improve disease specific or overall survival
        - recently, early initiation of rituximab increased progression-free survival (long-term outcome undetermined)
      - Start therapy only in presence of symptoms:
        - "B" symptoms
        - blood cell line dyscrasias
        - bulky disease
        - organ compression
        - ascites, pleural effusion
        - rapid progression
      - Complete remission with long progression-free survival requires:
        - Rituximab + chemotherapy

        - Chemotherapy regimens include:
            - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
            - CVP (cyclophosphamide, vincristine, prednisone)
            - FM (fludarabide, mitoxanatrone)
            - Bendamusdine
        - Antibody monotherapy (rituximab + radiotherapy or chlorambucil + rituximab) used in patients at low risk and when intense chemotherapy contraindicated
    - Response evaluation
        - Adequate radiologic studies midterm and after completion of chemotherapy
        - PET scan investigational until further studies confirm utility
    - Consolidation (once remission achieved, to sustain remission) and Maintenance
        - Rituximab for 2 years increases progression-free survival
        - Radiotherapy improves progression-free survival after chemotherapy, but unknown if it improves this parameter after rituximab
- Relapsed Disease
    - Repeat biopsy necessary to rule out aggressive lymphoma transformation
    - Salvage therapy depends on prior treatment response
        - Early relapse (under 12 months)
            - Non-cross resistant regimen (bendamustine after CHOP or vice-versa)
            - Add Rituximab if prior antibody treatment obtained over 6-12 months of remission
            - Radioimmunotherapy used for elderly and patients unable to tolerate chemotherapy
                - Radioisotope-labeled antibody kills cells and neighbors to which it is linked
                    - Yttrium-90-labeled ibritmomab tiuxetan
                    - Iodine-131-labeled tositumomab
            - Rituximab maintenance for 2 years increases progression-free survival and overall survival
        - High dose chemotherapy followed by autologous stem cell transplant should be considered in patients with short-lived remission from initial therapy

- Diffuse Large B-cell[9]
  - Age-stratified treatment regimens
    - Young, low and low-intermediate risk (International Prognostic Index (IPI) $\leq$ 1)
      - All stages
        - CHOP, 6-8 cycles + Rituximab, 6-8 doses
        - No proven benefit of radiotherapy consolidation to initial site
    - Young, high and high-intermediate risk patients (IPI $\geq$ 2)
      - No standard with sufficient efficacy
        - Same treatment as above generally applied
        - No proven benefit of radiotherapy consolidation
    - Ages 60-80
      - CHOP, 8 cycles + Rituximab, 8 doses
      - No proven benefit of consolidation via radiotherapy
    - Age > 80
      - Rituximab + attenuated chemotherapy shown to induce complete remission and long disease free survival in some elderly patients
  - Extra-nodal Disease
    - CNS involvement must be treated with high dose methotrexate
    - Adding cytarabide improves remission rate and outcome
  - Response evaluation
    - Abnormal radiologic exams repeated after 3-4 cycles and after last cycle
    - Bone marrow biopsy repeated after treatment only if involved at diagnosis
    - PET recommended after completion of therapy to define remission
  - Relapsed and Refractory Diffuse Large B cell Lymphoma
    - Over 30% of cases will relapse; confirmation of histology recommended (required if relapse after 12 months from initial diagnosis)
    - Assumes patient underwent adequate Rituximab-associated anthracycline-containing first line therapy
    - Age under 65-70 + no major organ disease (Salvage therapy):
      - Rituximab + chemotherapy followed by high-dose stem cell support (in those who respond to Rituximab + chemotherapy)
        - High dose stem cell support usually BEAM (Carmustine, Etoposide, Cytosine-arabinoside, Melphalan)
        - If non-candidate for high dose, other regimens available
    - Response evaluation:
      - Response criteria similar to those of first line therapy

        - Assess after 3-4 cycles of salvage therapy (prior to high-dose therapy) and at end of therapy
        - PET results before high-dose therapy correlate with clinical outcomes
- Marginal Zone[10]
    - Gastric MALT lymphoma
        - Stage I
            - Antibiotic eradication of H. Pylori with endoscopy
        - Stage II
            - Radiation therapy or rituximab
            - Endoscopy for re-staging
                - Re-treat H. Pylori as indicated
                - If no response, radiation therapy (RT) if not done previously
                    - With previous RT, treat as follicular lymphoma
        - Stage III-IV (advanced end-stage)
            - No set guidelines. Find clinical trial if available. Otherwise observe, treat symptomatically.
    - Nongastric MALT lymphoma
        - Stage I-II
            - Involved field radiotherapy or surgical resection
                - Follow with locoregional RT for positive surgical margins
        - Stage III-IV (extranodal disease with multiple nodal sites)
            - Treat as stage III-IV follicular lymphoma
    - Splenic Marginal Zone lymphoma
        - If pt. is asymptomatic with no splenomegaly, observe
        - If pt. has splenomegaly, treat for Hepatitis C if present.
            - If pt. has cytopenias, splenectomy or rituximab.
            - If progressive disease, treat per stage III/IV follicular lymphoma guidelines.
- Mantle Cell[10]
    - Management similar for all stages
        - Induction
            - Aggressive therapies
                - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
                - NORDIC (cyclophosphamide, vincristine, doxorubicin, prednisone alternating with rituximab and high-dose cytarabine)
                - CALGB- MTX + CHOP with rituximab
            - Less aggressive therapies
                - Bendamustine + rituximab
                - CHOP + rituximab

        - Cladribine + rituximab
        - CVP (cyclophosphamide, vincristine, prednisone) + rituximab
    - Consolidation
        - High dose therapy with autologous stem cell rescue
            - RCHOP
            - Multiple clinical trials available
    - Relapse/second-line therapies
        - Radiotherapy
        - Bendamustine + rituximab
        - Bortezomib + rituximab
        - Cladribine + rituximab
        - Allogeneic stem cell transplant (nonmyeloablative or myeloablative)

Follow-Up

1. Return to Office
    - Follicular[11]
        - History, PE every 3 months for 2 years; every 4-6 months for following 3 years and then annually (screen for transformation to aggressive nature and secondary malignancies)
        - CBC, Chemistries every 6 months for 2 years followed by as needed for suspicious symptoms
        - Radiologic exams every 6 months for 2 years and then annually; regular CT scans not mandated outside of clinical trials
        - Thyroid evaluation at 1, 2 and 5 years status post neck irradiation
    - Diffuse Large B-cell[12]
        - History, PE every 3 months for first year, then every 6 months for 2 additional years, then annually (screen for secondary tumors and long-term chemotherapy side effects)
        - CBC, LDH at 3, 6, 12 and 24 months, then as needed for suspect symptoms or clinical findings in patients who are candidates for further therapy
        - Pertinent radiologic exams at 6, 12 and 24 months from end of therapy; CT usual practice, but no evidence that patients in complete remission have improved outcomes with CT surveillance
        - Routine PET scans not recommended
    - Marginal Zone, Mantle Cell [10]
        - Clinical follow-up every 3-6 months for 5 years, then yearly or as clinically indicated
            - Diagnostic tests and imaging as indicated
                - Routine imaging not shown to improve ultimate outcome.

Prognosis

1. General
    - International Non-Hodgkin Lymphoma Prediction Factors[13]
        - Prognostic factors based on
            - Age (<60 vs >60)
            - Tumor Stage (I-IV)
            - Number of extranodal sites (<1 site vs >1site)
            - LDH value (<1 x normal vs >1 x normal)
            - Performance status (0 or 1 vs. 2-4)
2. Follicular[14]
    - Median survival 10 years; improved since use of rituximab
        - Stage I and II treated with radiotherapy - 40% durable remission rate
            - Survival comparable in those with no treatment and immediate treatment
        - Stage III and IV treated with radiotherapy – lasting disease remission with relatively low toxicity
        - Stage III and IV treated with immunochemotherapy – high response rates and prolonged remission periods (PFS 12-37 months.)
3. Diffuse Large B-cell[15]
    - Low-risk
        - 65% 5-year survival rate
        - Mean survival 8.7 years
    - Moderate-risk
        - 49% 5-year survival rate
        - Mean survival 7.1 years
    - High-risk
        - 15% 5-year survival rate
        - Mean survival 3.8 years
4. Marginal Zone[16]
    - Splenic
        - Good prognosis, 5-year cause-specific survival of 76%.
    - Gastric MALToma- 87% long-term disease-free survival with radiotherapy.
    - Non-Gastric MALToma- excellent prognosis
        - Complete response rate 99%
        - 10-year relapse-free rate 77%
        - 10 year overall survival rate 87%
5. Mantle Cell
    - Low-grade[17]
        - 6-year overall survival rate- 53%
            - 71% with radiotherapy
            - 25% without radiotherapy
    - High-grade[18]
        - 5-year survival rate- 47%
        - Median overall survival- 4.8 years

Prevention

1. Post therapy - annual influenza and appropriate interval pneumococcal immunizations recommended

Patient Education

1. The Leukemia and Lymphoma Society
    - http://www.lls.org/diseaseinformation/lymphoma/
2. National Cancer Institute
    - http://www.cancer.gov/cancertopics/types/non-hodgkin

References

1. Morschhauser F, et al. Rationale for Consolidation to improve Progression-Free Survival in Patients with Non-Hodgkins Lymphoma: A Review of the Evidence. The Oncologist 2009;14 (suppl 2):17-29.
2. Ansell SM, Armitage JO. Non-Hodgkin Lymphoma: Diagnosis and Treatment. Mayo Clnc Proc 2005; 80(8):1087-97.
3. Lenz G, Staudt LM. Aggressive Lymphomas. NEJM 2010; 362(15): 1417-1429.
4. National Cancer Institute Surveillance Epidemiology and End Results. Website.http://seer.cancer.gov/statfacts/html/nhl.html. Accessed May 9, 2012.
5. Bofetta P. Epidemiology of Adult non-Hodgkin Lymphoma. Ann Onc 2011; 22(Supp 4): iv27-iv31.
6. Wang S, Nieters A. Unraveling the interactions between environmental factors and genetic polymorphisms in non-Hodgkin lymphoma risk. Expert Reviews: Anticancer Therapy. 2010;10(3), 403-413.
7. Haddy R, Haddy T. Lifetime Follow-up Care after Childhood Cancer. JABFM, Sep-Oct 2010. Vol. 23, No. 5. pp. 647-654.
8. Dreyling M, et al. Newly Diagnosed and Relapsed Follicular Lymphoma: ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-up. Ann Onc 2011;22(Supp 6):vi59-vi63.
9. Tilly H, Dreyling M. Diffuse Large B-cell non-Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Onc 2010;21(Supp 5): v172-v174.
10. Zelenetz, Andrew, et al. NCCN Clinical Practice Guidelines in Oncology- Non-Hodgkins' Lymphomas. J Natl Compr Canc Netw 2011; May;9(5):484-560.
11. Dreyling M, et al. Newly Diagnosed and Relapsed Follicular Lymphoma: ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-up. Ann Onc 2011;22(Supp 6):vi59-vi63.
12. Tilly H, Dreyling M. Diffuse Large B-cell non-Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Onc 2010;21(Supp 5): v172-v174.
13. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A Predictive Model for Aggressive Non-Hodgkins Lymphoma. N Engl J Med 1993; 329:987-994.
14. Hitz F, et al. Diagnosis and Treatment of Follicular Lymphoma. Swiss Med Weekly 2011;141:w13247.
15. Izidore L. Prediction of Survival in Diffuse Large-B-Cell Lymphoma Based on the Expression of Six Genes. N Engl J Med 2004; 350:1828-1837.

16. Kahl B, Yang D. Marginal Zone Lymphomas: Management of Nodal, Splenic, and MALT NHL. Hematology 2008.
17. Leitch HA, et al. Limited-stage mantle cell lymphoma. Ann Oncol. 2003 Oct;14(10):1555-61.
18. Herrmann A, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol. 2008;27:511-518.

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