Overview of Follicular Non-Hodgkin Lymphoma

Susan Blumel, RN, BSN, OCN, CCRC
Clinical Research Nurse
University of Nebraska Medical Center

The Lymphatic System

• Primary Lymphoid Organs
  – Bone marrow
  – Thymus

• Secondary Lymphoid Organs
  – Spleen
  – Lymph nodes
  – Accessory lymphoid tissue

The NHLs are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment


Updated REAL/WHO Classification

B-cell neoplasms

• Precursor B-cell neoplasm: Precursor B-lymphoblastic leukemia and lymphoma

• Mature (peripheral) B-cell neoplasms:
  – B-cell CLL/SLL
  – B-cell prolymphocytic leukemia
  – Lymphoplasmacytic lymphoma/immunocytoma
  – Mantle cell lymphoma
  – Follicular lymphoma
  – Extra nodal marginal zone B-cell lymphoma of MALT type
  – Nodal marginal zone B-cell lymphoma (± monocytoid B-cells)
  – Splenic marginal zone lymphoma (± villous lymphocytes)
  – Hairy cell leukemia
  – Plasmacytoma/plasma cell myeloma
  – Diffuse large B-cell lymphoma
  – Mediastinal large B-cell lymphoma
  – Intravascular large B-cell lymphoma
  – Burkitt’s lymphoma

T-cell and putative NK-cell neoplasms

• Precursor T-cell neoplasm: Precursor T-lymphoblastic leukemia and lymphoma

• Mature (peripheral) T-cell and NK-cell neoplasms:
  – T-cell prolymphocytic leukemia
  – T-cell granular lymphocytic leukemia
  – Mycosis fungoides/Sézary syndrome
  – Peripheral T-cell lymphoma, not otherwise characterized
  – Hepatosplenic T-cell lymphoma
  – Subcutaneous panniculitis-like T-cell lymphoma
  – Angioimmunoblastic T-cell lymphoma
  – Extra nodal T-/NK-cell lymphoma, nasal type
  – Enteropathy-type intestinal T-cell lymphoma
  – Adult T-cell lymphoma/leukemia (HTLV 1+)
  – Anaplastic large cell lymphoma, primary cutaneous type
  – Anaplastic large cell lymphoma, nasal type
  – Anaplastic large cell lymphoma, salivary gland-type
  – Anaplastic large cell lymphoma, angioimmunoblastic type
  – Anaplastic large cell lymphoma, null cell type
  – Anaplastic large cell lymphoma, lymphoepithelioid type
  – Anaplastic large cell lymphoma, mixed cell type
  – Anaplastic large cell lymphoma, diffuse large cell type
  – Anaplastic large cell lymphoma, not otherwise specified
  – Angioimmunoblastic T-cell lymphoma
  – NK/T-cell lymphoma

Follicular lymphoma:
  – Low grade follicular lymphoma
  – Intermediate grade follicular lymphoma
  – High grade follicular lymphoma

Updated REAL classification NHL subtypes

<table>
<thead>
<tr>
<th>NHL Subtype</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>DLBCL</td>
<td>31%</td>
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<tr>
<td>MCL</td>
<td>6%</td>
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Frequency of REAL classification NHL subtypes

N = 1403


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NHL Epidemiology

- Most common hematologic cancer
- Prevalence ~300,000 patients
- Estimated new cases and deaths from non-Hodgkin's lymphoma (NHL) in the United States in 2005
  - New cases: 56,390.
  - Deaths: 19,200.
- Overall incidence has doubled since 1970's
- Increasing incidence of non–AIDS-associated NHL

Cancer Statistics, CA A Ca Jour for Clin, 2005

Diagnostic Workup

- LN Biopsy – Morphology, immunophenotyping, genetic testing
- H & P – LN enlargement, fever, weight loss, night sweats, PS, prognostic indicators
- Laboratory – CBC with diff, Platelets, Comprehensive chemistry panel (renal, liver, LDH), B2-microglobulin
- Imaging studies – CT scan, PET scan, MRI
- Bone marrow biopsy
- Lumbar puncture – if indicated

Adapted from NCCN Clinical Practice Guidelines, v. 1.2005

Ann Arbor Staging

- Stage I: Involvement of a single lymph node region (I) or single extralymphatic site (IE)
- Stage II: Involvement of ≥2 lymph node regions on the same side of the diaphragm (II) or involvement of limited or contiguous extralymphatic tissue (IIE) or spleen (IIS)
- Stage III: Involvement of lymph node regions on both sides of the diaphragm (III) which may include the spleen (IIIS), contiguous extralymphatic site (IIES) or both (IIIES)
- Stage IV: Diffuse or disseminated foci of involvement of ≥1 extralymphatic sites ± associated lymph nodes

International Prognostic Index (IPI)

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<tr>
<td>Age</td>
<td>≤ 60 versus ≥ 60 years</td>
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<tr>
<td>ECOG performance status</td>
<td>0-1 versus &gt;1</td>
</tr>
<tr>
<td>LDH</td>
<td>Normal versus elevated</td>
</tr>
<tr>
<td>Extranodal sites</td>
<td>0-1 versus &gt;1</td>
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<tr>
<td>Stage</td>
<td>I-II versus III-IV</td>
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Number of Factors Present | Risk Group | 5-year DFS (%) | 5-year OS (%) |
--------------------------|------------|----------------|---------------|
0-1                       | Low        | 70             | 73            |
2                         | Low-intermediate | 73             | 51            |
3                         | High-intermediate | 80             | 43            |
4-5                       | High       | 51             | 26            |

Follicular Lymphoma

- 2nd most common NHL subtype
- B-cell origin
- Common in elderly
- Indolent in nature
- Often asymptomatic with waxing and waning course
- 80% are stage III-IV at diagnosis
- Median survival from diagnosis: 10 years
- Incurable


Follicular Lymphoma: Duration of Chemotherapy-Induced Remissions

- Grade 1 (<5 lc/hpf)
- Grade 2 (5-15 lc/hpf)
- Grade 3 (>15 lc/hpf)

Gene Expression Profiling for Follicular Lymphoma
- Provides biological information not obtained with standard histologic classification and clinical evaluation
- Might provide improved prognostic information compared with standard evaluation
- Identifies potential therapeutic targets
- Clinical utility still being investigated
Gene Expression: Follicular NHL

Image Not Available

Application of Gene Expression Profiling for Follicular NHL

- Clinical Aggressiveness
- Risk of Transformation
- Response to rituximab

Blood 105:301, 2005
PNAS 99:8886, 2002
PNAS 100:1926, 2003

FL – Principles of Therapy

- Not curable with conventional therapy
- Response duration is generally shorter with each course of therapy
- Enrollment on clinical trials is recommended if feasible
- Patients may have significant co-morbid conditions complicating therapeutic options
- Observation is appropriate if there are no indications for therapy

NCCN Clinical Practice Guidelines, v. 1.2005

Indications for Therapy in FL

- Symptoms attributable to disease
- Threatened end-organ function
- Cytopenias secondary to BM infiltration
- Bulk at presentation
- Steady progression during a period of observation >6 months
- Patient preference

NCCN Clinical Practice Guidelines, v. 1.2005

Initial Therapy for FL - Stage I, II

Locoregional RT
OR
*Chemotherapy followed by RT
OR
*Extended-field RT
* can improve FFS, but not shown to improve OS

NCCN Clinical Practice Guidelines, v. 1.2005

Initial Therapy for FL - bulky stage II, III or IV

- Local RT
- Rituximab
- Chlorambucil
- Cyclophosphamide
- CVP (cyclophosphamide, vincristine, prednisone)
- Fludarabine +/- rituximab
- FND (fludarabine, mitoxantrone, dexamethasone) +/- rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) +/- rituximab
- Clinical Trial

NCCN Clinical Practice Guidelines, v. 1.2005
Nursing Considerations for Patient-Specific Immunotherapy

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Vaccine therapy requires……
• Approximately 1 year of treatment or longer
• Significant patient involvement
• A nursing plan/protocol
  – Tumor tissue acquisition
  – Patient scheduling
  – Vaccine administration
  – Toxicity management
  – Patient education

Tumor Acquisition
• Facilitate proper collection and handling of tumor tissue for vaccine production
  – Develop plan within your facility
• Send tumor tissue to manufacturing facility
• Ensure tissue adequacy prior to treatment start
Patient Scheduling

- Allow for post-chemo rest period
- Outpatient visits
  - Day 1
    - Lab and physical evaluation
    - Id-KLH and GM-CSF administration
  - Day 2-4
    - GM-CSF (may be self-injected)
    - Possible boosters
- Immune response measurements
- Post-treatment evaluation/follow-up

Vaccine Administration

- Identify injection site
  - Two separate injection sites in bilateral anterior thighs
  - Choose a site without redness or induration from prior vaccine series
  - All components (antigen, carrier and adjuvant) should be injected at the same site during each series
- Slow subcutaneous administration
- Use gauze pad to apply light pressure after injection

Potential Treatment Toxicities

- Injection site reactions
  - Edema
  - Erythema
  - Pruritis
- Flu-like symptoms (fever, chills, sweats, myalgias)
- Hypersensitivity reactions/Rash
- Fatigue
- Autoimmune considerations

Key Educational Points

- Vaccine mechanism of action
  - Use pictures
  - Use simple terms
  - Compare and contrast to preventative vaccines
- Toxicities
  - Let patients know about expected toxicities
  - OTC pain medication and/or ice
  - Nonsteroidal antipruritic cream
- Patient requires self-injection teaching
  - Provide supplies: alcohol preps, gauze, needles, syringes and biohazard needle containers, cool pack
  - Provide adjuvant in pre-filled and labeled syringes

Nursing Considerations

Summary

- Successful tumor acquisition for vaccine production requires a thoughtful plan
- Id-KLH active immunotherapy is easy to administer and well tolerated
- Patient education resources help you and your patient

Future Directions

- Application in relapsed vs. untreated disease
- Aggressive NHL
- Other B-cell malignancies
- Combination therapies
- Evaluation of new formulations and improved adjuvants

Genitope 9902: Aggressive B-Cell Lymphoma

Favld™ Phase 2 Trial: Post-Autologous SCT

- 5 monthly vaccinations starting a median of 5 months post-ASCT
- Demonstrated patients can generate immune responses after high-dose chemo and ASCT

Pilot Study: Idiotype Vaccine Study for First Relapse of Follicular Lymphoma

Acknowledgements