Indolent Non-Hodgkin Lymphoma: A Brief Overview of Management

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  – Abbvie
  – Janssen
  – Celgene
Presentation Overview

- Overview of Lymphoma
- Common Management Strategies and Outcomes
- New Developments
- Clinical Trials
- Questions
Lymphoma Overview

• Lymphoma is a hematologic malignancy (i.e., blood cancer) that arises from malignant transformation of peripheral blood, lymphatic system, and other bone marrow derived cells

• Over 70,000 new cases of lymphoma are diagnosed each year in the US

• Diverse group of diseases, comprising over 60 different subtypes of non-Hodgkin and Hodgkin lymphoma
Lymphoma Overview

Lymph Node
NHL Epidemiology

United States

~4% compound annual increase in incidence

Estimated annual incidence
Risk Factors

- Immunodeficiency disorders
- Autoimmune disorders
- Organ transplantation
- Radiation exposure
- Bacteria or viruses
- Environmental exposure?
Symptoms

- Swelling of lymph nodes (often, but not always painless)
- Fever
- Night sweats
- Unexplained weight loss
- Lack of energy
Diagnosis

- Physical examination
  - Lymphadenopathy, splenomegaly
- Biopsy
  - Adequate tissue is imperative
  - Excisional biopsy (optimal)
  - Multiple core biopsies may be acceptable
  - Fine needle aspiration is unacceptable
- Adequate immunophenotyping
  - Immunohistochemistry of paraffin sections
  - Flow cytometry to detect cell surface markers
- Cytogenetics/FISH to detect genetic abnormalities when appropriate
Stage

- **Stage I** - in a single lymph node or in one organ or area outside the lymph node
- **Stage II** - two or more lymph node regions on one side of the diaphragm
- **Stage III** - lymph nodes above and below the diaphragm
- **Stage IV** - in one or more organs or tissues (in addition to the lymph nodes); liver, blood or bone marrow
How Does One Decide Which Treatment to Recommend?

- Classification
  - Subtype

- Growth rate (grade)
  - Indolent vs. Aggressive

- Stage of disease
  - Local, distant, widespread

- Prognostic Factors
  - IPI, FLIPI, MIPI

- Disease Burden
  - GELF criteria
Indolent NHL: Common Management Strategies and Outcomes
NHL Subtypes

- Diffuse large B cell (DLBCL): 30%
- Mantle cell: 6%
- Follicular: 25%
- Small lymphocytic: 7%
- Mantle cell: 6%
- Burkitt: 2.5%
- T and NK cell: 12%
- Other subtypes: 9%
- MALT-type marginal-zone B cell: 7.5%
- Nodal-type marginal-zone B cell: <2%
- Lymphoplasmacytic: <2%
Indolent NHL

Hodgkin Lymphoma

Non-Hodgkin Lymphoma

T-cell Lymphoma

B-cell lymphoma

Indolent Lymphoma

Follicular Lymphoma

Marginal Zone Lymphoma

Aggressive Lymphoma

CLL/SLL
Treatment Options for Untreated Follicular Lymphoma

After Staging Evaluation

- Limited stage
  - XRT
- Advanced stage low tumor burden
  - Observation
  - Therapy
    - Rituximab
    - Clinical Trial
- Advanced stage high tumor burden
  - Chemo-immuno-therapy
Initial Treatment of FL in the US

A. Initial Treatment - All Patients
   - Clinical trial: 6.1%
   - Other: 1.6%
   - Observation: 17.7%
   - Chemotherapy: 3.2%
   - Radiotherapy: 5.6%
   - Rituximab monotherapy: 13.9%
   - Chemotherapy + rituximab: 51.9%

B. Initial Treatment - Stage I Patients
   - Clinical trial: 2.5%
   - Other: 2.1%
   - Observation: 28.7%
   - Chemotherapy: 30.4%
   - Radiotherapy: 23.4%
   - Rituximab monotherapy: 12.9%
Watchful Waiting

• “Watchful waiting” or “Watch and Wait”
  – Only for indolent, low-grade NHLs
  – Regular physical exam and lab evaluation
  – No treatment until patient has:
    • Symptoms- fever, chills, night sweats, weight loss
    • LN > 7 cm or ≥ 3 LNs > 3 cm in diameter
    • Splenomegaly
    • Cytopenias (anemia, thrombocytopenia), elevated LDH
    • Ascites or pleural effusion
  – Spontaneous regressions have occurred
The Natural History of Indolent NHL

Survival of Patients With Indolent Lymphoma:

<table>
<thead>
<tr>
<th>Era</th>
<th>Median OS</th>
</tr>
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<tbody>
<tr>
<td>Era 1</td>
<td>11.0 yrs</td>
</tr>
<tr>
<td>Era 2</td>
<td>11.0 yrs</td>
</tr>
<tr>
<td>Era 3</td>
<td>18.5 yrs</td>
</tr>
<tr>
<td>Era 4</td>
<td>Not reached</td>
</tr>
<tr>
<td>Overall</td>
<td>13.6 yrs</td>
</tr>
</tbody>
</table>

Horning SJ. *Semin Oncol.* 1993;20(suppl 5):75-88.

Tan D. *Blood.* 2013 Aug 8;122(6):981-7
Targeted Immune Therapy
Rituximab (Rituxan)

- Monoclonal antibody against CD20
- The first monoclonal antibody approved for use in cancer patients (1997)
- Given once per week for 4 weeks or in combination with standard chemotherapy
### Effect of Frontline Follicular Lymphoma Therapies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Colombat et al</th>
<th>Rummel et al.</th>
<th>Hiddemann et al</th>
<th>Marcus et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Bendamustine + Rituximab</td>
<td>CHOP + Rituximab†</td>
<td>CVP + Rituximab</td>
<td></td>
</tr>
<tr>
<td>Stage III/IV, %</td>
<td>50 (II+)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Grade 3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>9%</td>
</tr>
<tr>
<td>GELF Criteria for treatment, %</td>
<td>0</td>
<td>100</td>
<td>NR</td>
<td>80±</td>
</tr>
<tr>
<td>FLIPI ≥ 3, %</td>
<td>NR</td>
<td>46</td>
<td>NR</td>
<td>38</td>
</tr>
<tr>
<td>Bulky disease, %</td>
<td>0%</td>
<td>28</td>
<td>NR</td>
<td>39</td>
</tr>
<tr>
<td>ORR, %</td>
<td>73</td>
<td>94*</td>
<td>96</td>
<td>80</td>
</tr>
<tr>
<td>CR, %</td>
<td>26</td>
<td>41*</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>PFS</td>
<td>1 year 80%</td>
<td>2 year 78%*</td>
<td>2 year ≈ 85%</td>
<td>32 mo 50%</td>
</tr>
</tbody>
</table>

*Included indolent, MCL patients; †BLNI, ECOG Criteria; ‡70% had INF maint, 23% had SCT consolidation

Fowler, N. et al. ICML 2011. Abst#137
Dramatic Response to Therapy

3 cycles of BR
Chemo Side Effects

• Non-drug specific
  – Fatigue, loss of appetite, low energy
  – Nausea, vomiting
  – Low blood counts
    • White cells: risk of infections
    • Platelets: risk of bruising/bleeding
    • Red cells: anemia
  – Hair loss, skin and nail changes

• Chemo agent-specific
  – Doxorubicin- heart toxicity (heart failure)
  – Vincristine- nerve ending toxicity (neuropathy)
  – Prednisone- high blood sugar, agitation, loss of sleep, stomach irritation, “shakiness”
Rituximab Maintenance

HR = 0.55
95% CI: 0.44–0.68
p < 0.0001

Event-free rate

Time (months)

Patients at risk

<table>
<thead>
<tr>
<th>Rituximab</th>
<th>505</th>
<th>472</th>
<th>445</th>
<th>423</th>
<th>404</th>
<th>307</th>
<th>207</th>
<th>84</th>
<th>17</th>
<th>0</th>
<th>–</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>513</td>
<td>469</td>
<td>415</td>
<td>367</td>
<td>334</td>
<td>247</td>
<td>161</td>
<td>70</td>
<td>16</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

“Early” Progression is Associated with Poor Outcomes


R-Chop


R-Chop


B-R

Casulo. ASH 2013


Rituximab maintenance

Casulo. ASH 2013
Standard Treatment of Nodal iNHL

- Newly diagnosed iNHL
  - Stage I/II
    - Radiation Therapy
      - Observe Q 3-6mo
        - Yes
          - Treatment Rituximab BR RCHOP RCVP
            - CR
              - R-Maint
            - PR
              - R-Maint Observe
            - No Response
              - Salvage Chemo Consider SCT
        - No
          - Observe R-Maint
  - Symptoms*
    - Yes
      - Treatment Rituximab BR RCHOP RCVP
      - CR
        - R-Maint Observe
      - PR
        - R-Maint Observe
    - No
      - Observe R-Maint
Subsequent Therapy

- Rituximab
- Chemoimmunotherapy
  - BR
  - RCHOP
  - RCVP
  - RDHAP
  - RESHAP
  - RGDP
  - RICE
- Radioimmunotherapy
- Idelalisib
- Stem cell transplant for selected patients
Autologous Stem Cell Transplant: Procedure Overview

- Marrow harvesting
- High-dose chemotherapy and/or radiation conditioning regimen
- Stem cells may be purged
- Stem cells are cryopreserved
- Stem cells thawed
- Stem cells re-infused
Autologous Stem Cell Transplant

Fig 2. (A) Overall survival from date of diagnosis, by remission. (B) Overall survival from date of autologous stem cell transplantation, by remission.
Allogeneic Stem Cell Transplant

Procedure Overview

Patient

- High-dose chemotherapy and/or radiation conditioning regimen

Donor marrow harvesting

- Stem cell transplant

- Immunosuppression therapy to prevent GVHD
Allogeneic Stem Cell Transplant in Lymphoma

Figure 2. OS and PFS rates after NST with FCR conditioning.
New Developments in the Management of iNHL
Emerging Therapy for Lymphoma

Microenvironment
- IMiDs
- Immunotherapy

Chemotherapy
- Novel Combinations

Antibody Therapy
- Humanized CD20s
- Antibody conjugates

Cell Pathways
- Death receptor
- B-cell receptor
- NF-κB
PI3K Delta Inhibition in B-Cell Malignancies

PI3K Delta Pathway Drives

- Proliferation
- Cell survival
- Trafficking

Reference: Lannutti, Blood, 2011
PI3Kδ Inhibition with Idelalisib in Relapsed iNHL
Idelalisib in Rel/Ref FL

4 months of idelalisib
PI3Kδ Inhibition with Idelalisib+ R in Relapsed CLL
Targeting B-Cell Receptor Signaling: BTK

Antigen

B Cell Receptor

CD79B

CD79A

BTK

PI3K

PLCγ

BLNK

ERK

PIP3

DAG

IP3--Ca++

AKT

PKCβ

CARD11

Bcl10

MALT1

NFkB

MYD88

JAK1

IkB

Proteosomal Degradation

Transcriptional Activation

Cytokine Receptor

TLR

Antigen
Ibrutinib in R/R B-cell Malignancies

Advani. JCO. 2013
Ibrutinib versus Ofatumumab in relapsed CLL

Byrd. NEJM. 2014
Marked Reductions in Peripheral Lymphadenopathy Observed

Pretreatment

With Idelalisib Treatment

38-year-old patient with refractory CLL and 5 prior therapies
Antibody Therapy: Next Generation Molecules

- **Human IgG1 antibody**
- **Novel membrane-proximal small loop epitope**
- **Slow off-rate**
- **Induces ADCC**
- **Induces strong and rapid CDC**

Ofatumumab

- **OFATUMUMAB binding site**
- **RITUXIMAB binding site**

- **CD20 peptide**
- **Heavy chain**
- **Light chain**
- **Glycoengineering**

- **Human IgG, type II antibody**
- **Increased ADCC**
- **Lower CDC**
- **Glycoengineering for increased affinity to FcγRIIIa**

Image Courtesy of GlaxoSmithKline

Image Courtesy of Genentech
Mechanisms of Action of Lenalidomide in Lymphoma Cells and the Nodal Microenvironment

**T-Cell Effects**
- Activation and proliferation
- ↑ Immune synapse formation
- ↑ CD8+ T-effector cell activity
- Stimulation of cytotoxic CD8+ and helper CD4+ T cells
- ↑ Dendritic cell antigen presentation

**NK-Cell Effects**
- ↑ Number and activity of NK cells
- ↑ Enhanced ADCC
- ↑ Immune synapse formation and direct NK killing

**Malignant B-Cell Effects**
- ↑ p21\textsuperscript{WAF-1}, AP-1
- ↓ CDK2, CDK4, CDK6, Rb
- ↓ Akt, Gab1 phosphorylation
- ↑ G\textsubscript{0}/G\textsubscript{1} arrest; ↓ proliferation

**Microenvironment Effects**
- ↑ Anti-inflammatory cytokines: IL-2, IL-8, IL-10, IFN-γ, TNF-α
- ↓ Inflammatory cytokines: IL-1, IL-6, IL-12, TNF-α

Lenalidomide + Rituximab (R2) in Untreated Indolent Lymphoma: Response Rates

Lenalidomide + Rituximab in Indolent Lymphoma

Baseline

S/P cycle 6
Clinical Trials
Challenges to Progress

- No accepted standard of care
- Heterogeneous outcomes with frontline therapy
- Relapse/resistance
- Evolving understanding of lymphoma biology
Why Consider a Clinical Trial

- May offer additional or better options than standard therapy
- Advance the care for lymphoma
- Risks must be weighed against potential benefits
Progressive T cell dysfunction during chronic antigen exposure

Wherry, Nat Immunol, 2011
New Agents - Immunotherapy

Nastoupil, in press.

Pidilizumab + Rituximab in relapsed FL
66% ORR and 52% CR
Key Questions to Ask Your Doctor

• What type of lymphoma do I have? What is the specific subtype?
• Is it indolent or aggressive?
• What is the stage of my lymphoma?
• What are my treatment options?
• What side effects may I experience and how can I deal with them?
• Are there any clinical trials that I might benefit from, now or in the future?
Questions