FOLLOW UP CARE OF PATIENTS WITH
INDOLENT LYMPHOMAS

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Assistant Professor UBC, Hematology
## DISCLOSURES

<table>
<thead>
<tr>
<th>Disclosure</th>
<th>Companies</th>
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<tr>
<td>Any direct financial payments including receipt of honoraria</td>
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LEARNING OBJECTIVES

- Overview of indolent lymphoma subtypes
- Signs and symptoms of indolent lymphomas
- Survivorship, shared care and follow-up recommendations
OVERVIEW

Lymphoma

Non-Hodgkin Lymphoma (90%)
- Aggressive Lymphoma (50%)
  - DLBCL
  - Anaplastic large cell lymphoma
  - Mantle cell lymphoma
- Indolent Lymphoma (50%)
  - Follicular Lymphoma
  - Marginal Zone Lymphoma
  - CLL, SLL

Hodgkin Lymphoma (10%)
- Classical Hodgkin
OVERVIEW

Lymphoma

Non-Hodgkin Lymphoma (90%)

Aggressive Lymphoma (50%)
Curative 70%

Indolent Lymphoma (50%)
Curative <5% but survival measured in years/decades

Hodgkin Lymphoma (10%)

Classical Hodgkin
# Table of Contents

1. Introduction
   - Background
   - Objectives
2. Literature Review
   - Previous Studies
   - Methodological Framework
3. Methodology
   - Data Collection
   - Data Analysis
4. Results
   - Findings
   - Discussion
5. Conclusion
   - Implications
   - Recommendations
6. References
7. Appendix
   - Additional Information
8. Acknowledgments

**Table Legend**
- [ ] Indicates a table or figure
- [ ] Indicates a reference or citation
- [ ] Indicates a key term or concept

**Abbreviations**
- [ ] List of abbreviations

**Graphs and Figures**
- [ ] Diagrams
- [ ] Charts

**Tables**
- [ ] Table 1: Summary of Literature Review
- [ ] Table 2: Methodological Framework
- [ ] Table 3: Results Overview

**Figures**
- [ ] Figure 1: Conceptual Model
- [ ] Figure 2: Flowchart of Data Collection

**Keywords**
- [ ] Key terms
- [ ] Themes

**Supplementary Material**
- [ ] Supplemental Data
- [ ] Supplemental Tables

**Revision History**
- [ ] Initial Draft
- [ ] Final Draft

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[Note: The table above is a placeholder for the content of the document. The actual content is not available in the image provided.]
### WHO classification of the non-Hodgkin lymphomas (subclassified according to to clinical aggressiveness*)

<table>
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<th>The indolent lymphomas</th>
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<tr>
<td><strong>B-cell neoplasms</strong></td>
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<tr>
<td>Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia</td>
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<td>Lymphoplasmacytic lymphoma (i.e. Waldenstrom's macroglobulinemia)</td>
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<td>Plasma cell myeloma/plasmacytoma</td>
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<td>Hairy cell leukemia</td>
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<tr>
<td>Follicular lymphoma (grade I and II)</td>
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<td>Marginal zone B-cell lymphoma</td>
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<td>Mantle cell lymphoma*</td>
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<th><strong>T-cell neoplasms</strong></th>
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<tr>
<td>T-cell large granular lymphocyte leukemia</td>
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<td>Mycosis fungoides</td>
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<td>T-cell prolymphocytic leukemia</td>
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<td>Follicular lymphoma (grade III)</td>
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<td>Diffuse large B-cell lymphoma</td>
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<td>Anaplastic large cell lymphoma, T/null cell</td>
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<td>Burkitt's lymphoma</td>
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<td>Precursor B lymphoblastic leukemia/lymphoma</td>
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<td>Adult T-cell lymphoma/leukemia</td>
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<tr>
<td>Precursor T lymphoblastic leukemia/lymphoma</td>
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</table>
• Most common indolent subtypes:
  • Follicular Lymphoma
  • Marginal Zone Lymphoma (+subtypes)
  • Lymphoplasmacytic Lymphoma / Waldenstrom

• Others, not being discussed today:
  • CLL/SLL
  • Myeloma
  • Cutaneous T-cell lymphomas
CLINICAL PRESENTATION

- Lymphadenopathy (waxing and waning), but generally progressive
- Cytopenias
- Splenomegaly, hepatomegaly
- Skin rashes, renal impairment, excessive fatigue, etc.
- B-symptoms:
  - Fever >38°C
  - Weight-loss, >10% body-weight in past six months
  - Sweats, drenching
CLINICAL PRESENTATION

• Extranodal presentation:
  • CNS disease (almost always aggressive)
  • GI tract
  • Skin- or other organ-involvement
  • Bone marrow involvement
CLINICAL PRESENTATION

Associated emergencies:
- Spinal cord compression
- CNS mass (seizure, headaches, visual changes, etc.)
- Airway obstruction (mediastinal mass)
- Pericardial tamponade
- SVC obstruction
- GI-/renal-obstruction
- Tumor lysis syndrome (Ca, PO4, Creat, uric acid, LDH, etc.)
CLINICAL PRESENTATION

• Clinical exam:
  • Lymphoid survey:
    • Waldeyer’s ring
    • Peripheral lymphnode stations
    • Liver/spleen
    • Other (occipital, preauricular, epitrochlear, popliteal)
  • Chest/lung/cardiac
  • Abdomen/pelvis
CLINICAL PRESENTATION

- Investigations:
  - Imaging studies (CT with contrast)
  - Labs: CBC, diff, creatinine, LDH, electrolytes
  - Rule out other causes: infections, autoimmune,
- Lymph-node-biopsy: progressive size, persistent (>4-6 wks), enlarged (>2cm)
  - FNA ----- BAD!!!
  - Core Bx ----- GOOD
  - Excisional Bx ----- BEST!!!
Tissue diagnosis is paramount PRIOR to referral to oncologist!

- Without a definitive diagnosis, unable to provide treatment recommendation
- Differential diagnosis of lymphadenopathy is broad:
  - Infections
  - Reactive, drugs, etc.
  - Autoimmune
  - Sarcoid
  - Malignancy including lymphoma, solid cancer, etc.
Follicular Lymphoma - 1.

**Image ID:** 2050  
**Authors:** Marshall Kadin

**Category:** Lymphoma: Mature B-cell and Plasma cell Neoplasms > Low-grade B-cell lymphoma > Follicular Lymphoma
STAGING
Non-Hodgkin Lymphoma (NHL) Stages

**Stage I**
Localized disease; single lymph node region or single organ

**Stage II**
Two or more lymph node regions on the same side of the diaphragm

**Stage III**
Two or more lymph node regions above and below the diaphragm

**Stage IV**
Widespread disease; multiple organs, with or without lymph node involvement
Once diagnosis is established, refer to Oncology

Additional testing might include:

- PET, bone marrow, labs, Hep, HIV, echo, …
- Ancillary tests determine stage, prognosis, fitness for treatment, etc.
PROGNOSIS

- FLIPI (follicular lymphoma international prognostic index):
  - Age >60
  - Number of nodal sites >4
  - LDH elevated
  - Hemoglobin <120
  - Stage III/IV

10 year survival: low risk 70%; high risk 35%
TREATMENT

- Depending on staging investigations and patient factors:
  - Radiation in curative intend (limited tumor burden!)
  - Watch & wait in asymptomatic advanced stage
  - Single agent Rituximab in asymptomatic advanced stage

- **Chemo-immunotherapy in symptomatic patients**
TREATMENT

• Current “standard” chemo-immunotherapy:
  • Bendamustine + Rituximab (x6 cycles; 6 months)
  • Rituximab maintenance (x8 cycles; 24 months)
    • STIL trial: response rate >90%; median PFS: 69.5 months, estimated survival at 10 years: 71%
StiL NHL 1-2003: BR vs R-CHOP in Newly Diagnosed FL

- Randomized, open-label phase III noninferiority trial
  - Primary endpoint: noninferiority of BR vs R-CHOP for PFS (decrease < 10% at 3 yrs)

  Stratified by histological subtype

  Treatment-naive patients with MCL or indolent CD20-positive lymphoma, including FL (N = 549)

  BR (n = 274*)

  R-CHOP (n = 275†)

  *n = 261 assessed. †n = 253 assessed.

- No OS difference between arms
- Toxicity less with BR (SAEs: 19% vs 29% with R-CHOP)

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Slide credit: clinicaloptions.com
Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

Carla Casulo, Michelle Byrtek, Keith L. Dawson, Xiaolei Zhou, Charles M. Farber, Christopher R. Flowers, John D. Hainsworth, Matthew J. Maurer, James R. Cerhan, Brian K. Link, Andrew D. Zelenetz, and Jonathan W. Friedberg
Fig 1. CONSORT diagram for participant selection. One patient who experienced progression of disease (POD) before receiving rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was excluded. FL, follicular lymphoma; NLCS, National LymphoCare Study; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine.

Published in: Carla Casulo; Michelle Byrtek; Keith L. Dawson; Xiaolei Zhou; Charles M. Farber; Christopher R. Flowers; John D. Hainsworth; Matthew J. Maurer; James R. Cerhan; Brian K. Link; Andrew D. Zelenetz; Jonathan W. Friedberg; Journal of Clinical Oncology 2015 332516-2522.
DOI: 10.1200/JCO.2014.59.7534
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Peak risk of progression is within the first 24 months of Dx

Fig 2. Estimated hazard of progression for the (A-C) National LymphoCare Study and (D) University of Iowa and Mayo Clinic Molecular Epidemiology Resource validation cohorts. (A) Rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP); (B) rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); (C) rituximab with fludarabine (R-Flu); (D) validation set (R-CHOP).
Fig 3. (A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group. Patients with early progression of disease (POD) had poor survival. Two-year OS was 68% (95% CI, 58.2% to 76.3%). Five-year OS was 50% (95% CI, 39.4% to 59.2%). OS in the reference group was 97% (95% CI, 94.6% to 98.1%) at 2 years and 90% (95% CI 86.2% to 92.4%) at 5 years. (B) Patients in the validation set who received R-CHOP with early POD also had inferior OS.

Published in: Carla Casulo; Michelle Byrtek; Keith L. Dawson; Xiaolei Zhou; Charles M. Farber; Christopher R. Flowers; John D. Hainsworth; Matthew J. Maurer; James R. Cerhan; Brian K. Link; Andrew D. Zelenetz; Jonathan W. Friedberg; Journal of Clinical Oncology 2015 332516-2522.
DOI: 10.1200/JCO.2014.59.7534
Copyright © 2015 American Society of Clinical Oncology
Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma

The occurrence of early progression (POD24) may be decreasing following the introduction of BR, but the majority of POD24 patients have transformed lymphoma.

Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma

Ciara L. Freeman, Robert Kridel, Alden A. Moccia, Kerry J. Savage, Diego R. Villa, David W. Scott, Alina S. Gerrie, David Ferguson, Fergus Cafferty, Graham W. Slack, Pedro Farinha, Brian Skinnider, Joseph M. Connors, Laurie H. Sehn, Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma, Blood, 2019, Figure 1.
POST TREATMENT

• Historically, patients remain under care of Hematologist/Oncologist
  • Regular follow up of perfectly well patients every 3-6 months
  • Neglected other medical issues (HTN, DM, CAD, etc)
  • Lack of cancer screening
  • ++ referral to other specialist

• Patient experiences anxiety, travel to cancer clinic, parking, etc
POST TREATMENT

• Proposition:
  • Transfer of care to primary care provider of patients with indolent lymphomas after their initial treatment if they achieved a complete remission after 2.5 years

• Rational:
  • Excellent prognosis and low risk immediate lymphoma recurrence
  • Enable Hematologist/Oncologist to care for new patients/ patients on Tx
  • Decrease wait times for cancer patients
  • Decrease health care costs
SURVIVORSHIP

- **DISCLAIMER:**
  - Limited evidenced based guidelines
  - Level of evidence often: Expert Opinion
  - Extrapolation from Hodgkin Lymphoma survivors
# Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

<table>
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<tr>
<th>Examination</th>
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<th>Year 3-5</th>
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<td>History</td>
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<td>Every 3-6 months</td>
<td>Every 6-12 months</td>
<td>Annually</td>
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<td>Physical examination</td>
<td>Particular: peripheral LNs, liver, spleen</td>
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<td>Annually</td>
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<td>Laboratory work-up</td>
<td>Blood and differential count</td>
<td>Every 3-6 months</td>
<td>Every 6-12 months</td>
<td>Annually</td>
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<td>LDH, IgG levels</td>
<td>Every 3-6 months</td>
<td>Every 6-12 months</td>
<td>If progression suspected</td>
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<tr>
<td>Imaging (optional)</td>
<td>Abdominal ultrasound</td>
<td>Every 6 months</td>
<td>Every 12 months</td>
<td>If progression suspected</td>
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<tr>
<td></td>
<td>CT neck, chest, abdomen</td>
<td>Every 6-12 months</td>
<td>Every 12-24 months</td>
<td>If progression suspected</td>
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</table>

CT, computed tomography; IgG, immunoglobulin G; LDH, lactate dehydrogenase; LN, lymph node.
SURVIVORSHIP

- Relapsed lymphoma
  - Yearly physical exam, focusing on lymphnode exam, spleen, liver
  - History, B-symptoms
  - Labwork, CBC, diff, LDH

- Imaging???
Surveillance Imaging during First-Remission in Follicular Lymphoma Does Not Impact Overall Survival

Max L. Goldman, BA, Chaejin Kim, PharmD, Zhengjia Chen, PhD, Oscar Calzada, BS, Michael C Churnetski, BS, Christopher Flowers, MD, Jonathon B Cohen, MDMS,

Surveillance Imaging during First-Remission in Follicular Lymphoma Does Not Impact Overall Survival, Blood, 2017,
SUSPECTED RELAPSE

- Patient detects relapse in 71% (29% Medical Oncologist)*
  - No difference in survival!!!
- If relapse is suspected, repeat imaging and biopsy
- Contact Medical Oncologist
  - Multiple different treatment approaches:
    - Chemo-immunotherapy
    - radiation
    - Stem-cell transplantation

*Savage. et al.; Annals of Oncology
Volume 25, issue 5. 2013
SURVIVORSHIP

- Long term side effects (Hodgkin Lymphoma):
  - Secondary malignancies, ongoing screening
  - CVD
  - Immunosuppression: yearly flu shot, pneumococcal, shingles, COVID (booster!)
  - Cognitive deficits, chronic fatigue,
  - Psychosocial dysfunction

- There is limited data in long term side effects for Non-Hodgkin Lymphoma
Lymphoma diagnosis should be suspected: progressive adenopathy/ B-symptoms

Imaging studies and excisional biopsy are key in initial management

Patients who achieve a complete remission with first line therapy have an excellent prognosis

Post treatment follow up should include yearly physical exam focusing on lymphnode stations, basic labs (CBC, differential, LDH). Limited evidence for routine imaging studies

Suspected relapse should trigger imaging and repeat biopsy

Contact Medical Oncologist if questions or concerns
RESOURCES


• Phone:
  • Abbotsford: 604-851-4710
  • Kelowna: 250-712-3900
  • Prince-Georg: 250-645-7328
  • Surrey: 604-930-2098
  • Vancouver: 604-877-6098
  • Victoria: 250-519-5500
Kai.Luecke@bccancer.bc.ca

Please spare three minutes on a quick questionnaire about lymphoma:

https://surveys.vch.ca/Survey.aspx?s=6fffae5c0b7346d1a821ebcd26a3a510

Get a coffee card in appreciation of your input! (email to PQI@PHSA.CA)