FOLLOW UP CARE OF PATIENTS WITH INDOLENT LYMPHOMAS

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DISCLOSURES

Any direct financial payments including receipt of honoraria	AbbVie, Astra-Zeneca, Gilead, Janssen, Sanofi
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All other investments or relationships that could be seen by a reasonable, well-informed participant as having a potential to influence the content of the educational activity	

LEARNING OBJECTIVES

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





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Chronic lymphocytic leukemia/small lymphocytic	1 lymphoma
Monoclonal B cell lymphocytosis*	
B cell prolymphocytic leukemia	
Splenic marginal zone lymphoma	
Hairy cell leukemia	
Lymphoplasmacytic hymphoma	
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WHO classification of the non-Hodgkin lymphomas (subclassified according to to clinical aggressiveness*)

The indolent lymphomas	
B-cell neoplasms	
Small lymphocytic lymphoma/B-cell chronic lympho	ocytic leukemia
Lymphoplasmacytic lymphoma (± Waldenstrom's i	macroglobulinemia)
Plasma cell myeloma/plasmacytoma	
Hairy cell leukemia	
Follicular lymphoma (grade I and II)	
Marginal zone B-cell lymphoma	
Mantle cell lymphoma [¶]	
T-cell neoplasms	
T-cell large granular lymphocyte leukemia	
Mycosis fungoides	
T-cell prolymphocytic leukemia	
Natural killer cell neoplasms	
Natural killer cell large granular lymphocyte leuker	mia
he aggressive lymphomas	
B-cell neoplasms	
Follicular lymphoma (grade III)	
Diffuse large B-cell lymphoma	
Mantle cell lymphoma ¶	
T-cell neoplasms	
Peripheral T-cell lymphoma	
Anaplastic large cell lymphoma, T/null cell	
he highly aggressive lymphomas	
B-cell neoplasms	
Burkitt's lymphoma	
Precursor B lymphoblastic leukemia/lymphoma	
T-cell neoplasms	
Adult T-cell lymphoma/leukemia	
Precursor T lymphoblastic leukemia/lymphoma	

OVERVIEW

- 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

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

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

- Associated emergencies:
 - Spinal cord compression
 - CNS mass (seizure, headaches, visual changes, etc.)
 - Airway obstruction (mediastinal mass)
 - Pericardial tamponade .
 - SVC obstruction •
 - Gl-/renal-obstruction •
- Features of asseressive lymphomasi Tumor lysis syndrome (Ca, PO4, Creat, uric acid, LDH, etc.)

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



- 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



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TREATMENT

- 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)



*n = 261 assessed. ^{+}n = 253 assessed.

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



1. Rummel. Lancet. 2013;381:1203. 2. Rummel. ASCO 2017. Abstr 7501.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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 Copyright © 2015 American Society of Clinical Oncology

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).

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



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



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 bendamustinerituximab is associated with high risk of transformation in advanced stage follicular lymphoma, Blood, 2019,



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:
 - <u>Transfer of care to primary care provider of patients with indolent</u> <u>lymphomas after their initial treatment if they achieved a complete</u> <u>remission after 2.5 years</u>
 - 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 7. Recommended follow-up after end of therapy						
Examination	Details	Year 1-2	Year 3-5	Year >5		
History	B symptoms (see Table 2)	Every 3-6 months	Every 6-12 months	Annually		
Physical examination	Particular: peripheral LNs, liver, spleen	Every 3-6 months	Every 6-12 months	Annually		
Laboratory work-up	Blood and differential count LDH, IgG levels	Every 3-6 months Every 3-6 months	Every 6-12 months Every 6-12 months	Annually If progression suspected		
Imaging (optional)	Abdominal ultrasound	Every 6 months	Every 12 months	If progression suspected		
	CT neck, chest, abdomen	Every 6-12 months	Every 12-24 months	If progression suspected		
T. 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

Figure 1 — Descriptive Statistics Flow Chart



Figure 2 - OS for Clinical vs. Surveillance Method of Relapse Detection



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,

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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

SUMMARY

- Lymphoma diagnosis should be suspected: progressive adenopathy/ Bsymptoms
- 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

www.bccancer.bc.ca "Health Professional" – "Cancer Management Guidelines"

• 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

QUESTIONS

• 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 <u>POI@PHSA.CA</u>)