Waldenström Macroglobulinemia: The Burning Questions

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Morie Gertz MD, MACP

Are my kids going to get this?

- Familial seen in approximately 5–10% of all CLL patients and can be associated with earlier age of diagnosis, more female prevalence, and increased incidence of other lymphoproliferative disorders (LPD), such as non-Hodgkin Lymphoma. 6 per 100,000 persons per year

- In Sweden: first-degree relatives of LPL/WM patients to have 20-fold (4.1-98.4), 3.0-fold (2.0-4.4), 3.4-fold (1.7-6.6), and 5.0-fold (1.3-18.9) increased risks of developing LPL/WM, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and monoclonal gammopathy of undetermined significance (MGUS), respectively. Waldenstrom is about $4/10^6$/yr. a 20 fold rise would be $8/10^5$/yr

WM/LPL #2144 controls 8279

Relative risk of lymphoproliferative malignancies and MGUS among first-degree relatives of LPL/WM patients

	Risk among first-degree relatives								
	Relatives of LPL pts only			Relatives of WM pts only			Relatives of LPL/WM pts combined		
	Pts	Co	RR (95% CI)*	Pts	Co	RR (95% CI)*	Pts	Co	RR (95% CI)*
LPL/WM	4	1	16.6 (1.7-162.2)	6	1	24.0 (2.9-201.1)	10	2	20.0 (4.1-98.4)
Non-Hodgkin lymphoma	15	26	2.3 (1.2-4.3)	28	32	3.5 (2.1-5.8)	43	58	3.0 (2.0-4.4)
Chronic lymphocytic leukemia	7	6	4.8 (1.6-14.1)	9	13	2.7 (1.1-6.5)	16	19	3.4 (1.7-6.6)
Hodgkin lymphoma	3	2	5.9 (1.0-36.0)	1	19	0.2 (0.0-1.5)	4	21	0.8 (0.3-2.2)
Multiple myeloma	6	11	2.2 (0.8-5.9)	5	16	1.2 (0.4-3.3)	11	27	1.6 (0.8-3.2)
MGUS	2	1	8.1 (0.7-90.6)	3	3	4.0 (0.8-20.0)	5	4	5.0 (1.3-18.9)

RR indicates relative risk; CI, confidence interval; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; Pts, patients; and Co, controls.

*All estimates were adjusted for sex of first-degree relative.

My opinion

- first degree relatives can have a serum protein electrophoresis beginning at age 50 repeated every 2 years

How long will I live?

- Since I began practice the survival has more than doubled
- Half of patients with symptomatic WM succumb to the disorders associated with old age
- New drugs are being developed at a rapid pace
  - Oprozomib, IMO-8400, Lenalidomide & everolimus combinations, carfilzomib, bendamustine, ibrutinib
- The danger of medians
  - Height across populations & income

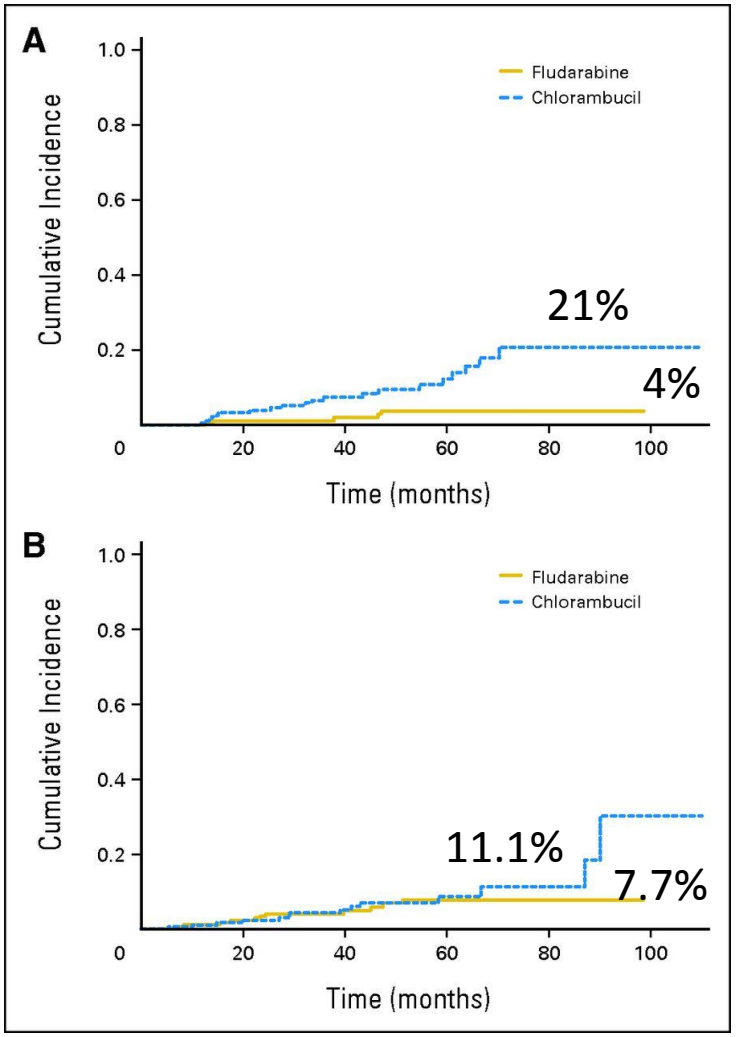
What can I do to live longer

- Life style
- Activity
- Nutrition
- Obesity & Chemotherapy
  - clear standards or dosing guidelines are unable to be made for the obese population
- Frailty
  - may be predictive of decreased cancer-independent survival

Will my WM transform into something worse?

- Richter's Transformation
  - tumor cells of DLBCL are clonally identical to those of WM/LPL.
  - occur in 6% of patients with WM
  - Role of nucleoside analogs
- MDS
  - Role of chemotherapy and DNA damage 1-3%

Cumulative incidence of (A) secondary malignancies and (B) high-grade lymphomas.



Leblond V et al. JCO 2013;31:301-307

Will I be Disabled?

- Fortunately the overwhelming majority of patients have complications limited to their blood counts and problems of the lymph nodes live & spleen are much less common
- Neuropathy
  - Not therapy related
- Renal Complications/amyloidosis
- Cryoglobulinemia

What are the complications that can be seen?

Classification	No.	%
Monoclonal gammopathy of undetermined significance (MGUS)	242	56 Ratio MGUS:WM=4:1
Waldenström's macroglobulinemia (WM)	71	17
Lymphoma (LY)	28	7
Chronic lymphocytic leukemia (CLL)	21	5
Primary amyloidosis (AL)	6	1
Lymphoproliferative disease (LP)	62	14
Total	430	100

The spectrum of IgM monoclonal gammopathy in 430 cases

	MGUS	WM	LY	CLL	AL	LP	Total
Palpable liver (%)	11	25	32	48	33	29	19
Palpable spleen (%)	6	20	29	62	17	34	17
Lymphaden opathy (%)	3	17	43	67	0	39	16

Five percent of all patients had a peripheral neuropathy; more than half the cases occurred in patients with MGUS.

	MGUS	WM	LY	CLL	AL	LP
Hemoglobin (g/dl)						
Median	13.6	10.0	12.7	10.9	13.0	10.9
Leukocytes ($10^3/mm^3$)						
Median	7.0	6.0	6.9	28.2	7.8	6.3
Serum M protein (g/dl)						
Median	1.5	4.3	1.3	1.2	1.4	2.0

	MGUS	WM	LY	CLL	AL	LP
No. of patients tested	200	60	21	17	5	51
IgG (%)						
Normal[†]	**64**	**31**	48	41	80	37
Increased	1	7	0	6	0	4
Decreased	**35**	**62**	52	53	20	59
IgA (%)						
Normal[‡]	91	78	81	76	60	67
Increased	3	2	0	6	0	4
Decreased	6	20	19	18	40	29

Impact of Uninvolved immunoglobulins

Viscosity in WM

	MGUS	WM	LY	CLL	AL	LP
No. of patients						
Tested	40	**51**	6	3	1	24
>4.0 cP	0	**15**	0	0	0	2[‡]
>1.8 cP	16	46	3	2	1	18
Viscosity (cP)						
Median	1.7	2.8	1.8	1.9	2.0	2.0
Range	1.0–2.9	1.2–14.8	1.3–2.8	1.8–2.8	2.0	1.2–6.5

Should I be tested for MYD88 L256P?

Lian Xu USA PB MYD88 testing for WM diagnosis

Great Debates in Waldenstrom's Macroglobulinemia

Chairs: Veronique Leblond and Shirley D'Sa

Should MYD88 and CXCR4 be tested in all WM patients?

Yes: Xavier Leleu

No: Eva Kimby

Sunday, August 17, 2014

8:00-12:00 **Task Force for Updating Recommendations for Diagnostic Workup of WM**

Chairs: Ranjana Advani and Stathis Kastritis

- **MYD88 is not currently part of the diagnostic criteria**
- **The clinical outcome of MYD88+WM & MYD88-WM is still not clarified so it is not as yet A validated prognostic factor**
- **Therapy as yet is not determined by MYD88 status**
- **Does not distinguish WM from IgM MGUS**
- **Not available in MML**

What are the Triggers for initiating therapy?

Second International Workshop on Waldenström's Macroglobulinemia agreed that initiation of therapy was appropriate for patients with constitutional symptoms such as **fever, night sweats, fatigue due to anemia, or weight loss**. The presence of **progressive, symptomatic lymphadenopathy or splenomegaly** provided additional reasons to begin therapy. The presence of anemia with a **hemoglobin value of 10 g/dL or lower or a platelet count lower than 100 × 10^9/L** due to marrow infiltration also justified treatment. Certain complications such as **hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia** may also be indications for therapy

Mayo Clin Proc. 2010 Sep;85(9):824-33.

What should I monitor when I see my Provider?

Watch & Wait; Prior Rx

- Hb
- Platelets
- M-Spike
- IgM
- ± Free light Chain
- Monitoring of liver spleen & lymph node size

On Active Rx

- The key monitoring metric should be driven by why therapy was initiated and corroborated by indirect measures of WM including IgM & M spike

Note bone marrow is not part of my routine monitoring schedule

Is Rituxan alone a good therapy?

- N=69 strictly defined WM
- Four doses of rituximab
- 50% fall in IgM in 19 (28%)
- 25-50% fall in IgM in 17 (25%)
- >25% reduction in IgM 36/69=52%
  - Chlorambucil single agent reduction of IgM >50%-39%
  - Fludarabine 48% (second cancers 3.7%)

J Clin Oncol. 2013 Jan 20;31(3):301-7

How deep a response do I need?

- Controversial and debates on depth of response are ongoing
- Unclear that adding new therapies to deepen response after a plateau has been achieved is indicated and its not part of my practice

Should I get a second opinion?

What's the deal with maintenance Rituximab

- Observational study R maint associated with improved outcomes but more frequent infections. No quality of life measure done
- In a survey performed in the Netherlands WM maintenance was recommended by 23% and actually used for their last patient in 8.5%-
- The National Institute for Health and Clinical Excellence (NICE) considered it impossible to draw firm conclusions regarding the clinical effectiveness of the intervention -2013

Results in FL

Table 2. Trials evaluating maintenance rituximab in patients with untreated follicular lymphoma

Study	No.	Induction regimen	Maintenance schedule	PFS or EFS (MR versus observation)	OS (MR versus observation)
Hochster *et al.* [11]	387	CVP	Four weekly doses every 6 months for 2 years	64%* vs 33% (3 years)	91% vs 86% (3 years)
Martinelli *et al.* [19]	202	R alone	Single dose at 3, 5, 7 and 9 months	24 months* vs 13 months	Difference not statistically significant
Ardeshna *et al.* [21]	720	R alone	Single dose every 2 months for 2 years	79% reduction in the risk of progression with MR*	Not reported
Salles *et al.* [13]	1217	R-CVP, R-CHOP or R-FCM	Single dose every 2 months for 2 years	74.9%* vs 57.6% (3 years)	Not significantly different between the two arms
Foa *et al.* [40]	545	Various R based regimens	Single dose every 2 months for 2 years	Not reported	Not reported
Vitolo *et al.* [25]	242	R-FND	Single dose every 2 months for four doses	80% vs 68% (2 years)	No data available

CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; FCM, fludarabine, cyclophosphamide, mitoxantrone; FND, fludarabine, mitoxantrone, dexamethasone; MR, maintenance rituximab; OS, overall survival; PFS, progression-free survival; R, rituximab.
*Statistically significant value.

How about Ibrutinib?

- **Approved from CLL**
- **1 prior treatment**
- **Intended therapy consisted of 420 mg of oral ibrutinib daily for 2 years.**
- **The best overall response rate i.e. minor response (MR) or better is 81% (4 VGPR; 32 PR, 15 MR), with a major response rate (PR or better) of 57.1% and a median time to response of 4 weeks.**