Updates in Indolent Lymphoma

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- No disclosures or conflicts of interest

Overview

- Follicular Lymphoma: Initial treatment

  Relapsed disease

- Lymphoplasmacytic Lymphoma/Waldenstrom's Macroglobulinemia

- Hairy Cell Leukemia

Follicular Lymphoma- Case 1

68 male presents in 2011 with fatigue, enlarged lymph nodes in neck and axilla

Excision biopsy of axillary lymph node shows Follicular Lymphoma grade 1-2/3

CT scan of Chest/Abd/Pelvis shows enlarged lymph nodes in the chest, axilla, upper abdomen, and pelvis (> 4 areas)

Blood counts normal. Hemoglobin 13. LDH 280 (elevated)

Bone marrow biopsy shows presence of FL (30%) marrow

Follicular Lymphoma- Case 1 (contd)

FLIPI score (Follicular Lymphoma International Prognostic Index)

Age > 60 (yes)

LDH (lactate dehydrogenase) > upper limit of normal (yes)

Hemoglobin > 12 (no)

Ann Arbor Stage III or IV (yes)

Number of involved areas > 4 (yes)

FLIPI high risk (has 4/5) factors

Follicular Lymphoma- Case 1 (contd)

- Does the patient need treatment: Yes. He has symptoms

Treatment: He was placed on ECOG 2408 study. Phase 2 three arm study

BR → R maintenance
BVR → R maintenance
BR → R + L maintenance

B (Bendamustine, TREANDA); R (Rituximab, RITUXAN)
V (Bortezomib, VELCADE); L (Lenalidomide, REVLIMID)

Follicular Lymphoma- Case 1 (contd)

- He was randomized to BR → R maintenance arm
- Received 6 cycles of BR. Tolerated well. Enlarged lymph nodes normalized clinically and on imaging. Bone marrow cleared.
- Tolerated rituximab maintenance well (borderline white count which improved once rituximab completed)
- Continues to be in complete remission

Discussion points

- Symptoms indicating immediate treatment (fever, night sweats, weight loss, fatigue, bothersome lymphadenopathy, low blood counts)
- What is initial frontline treatment in high FLIPI score FL (role of bendamustine)
- Role of lenalidomide
- Role of maintenance rituximab after chemotherapy

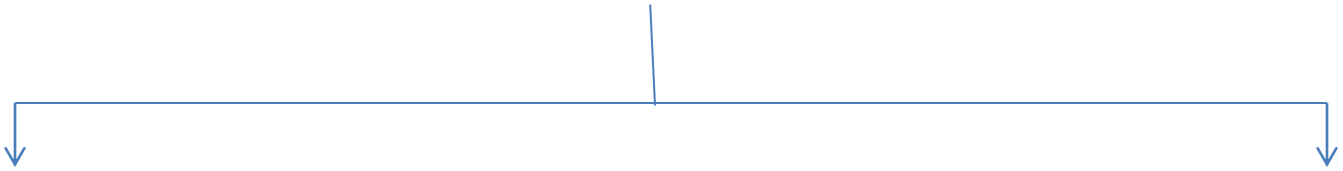
Role of bendamustine

German NHL1 study
514 patients with FL, iNFL (indolent non follicular lymphoma) and MCL

BR		RCHOP
94%	overall response rate	94%
40%	complete response rate	30%
70	progression free survival (months)	31
0%	alopecia when 3 or more cycles	100%
37%	infections	60%
7%	peripheral neuropathy	29%
30%	hematologic toxicity	68%
6%	mouth sores	19%
16%	rash/skin reactions	9%

Role of bendamustine

BRIGHT Study



BR		RCHOP RCVP
97%	Response Rate	92%
31%	Complete Response	25%
4%	Alopecia	50%/21%
12%	Peripheral neuropathy	45%
22%	Rash	14%

Role of Lenalidomide

- Oral immunomodulator
- FDA approved for multiple myeloma, a subtype of MDS and mantle cell lymphoma
- Has single agent activity but exciting in combination with rituximab
- M.D. Anderson study had 110 patients (FL 50). Overall response rate was 98% and complete response rate 87%.
- Significant adverse effects (neutropenia, rash, muscle pain, cough, dyspnea, faitigue, thrombosis)
- RELEVANCE: Ongoing phase 3 studies assessing R2 versus R-chemo (STAY TUNED!)

Rituximab maintenance after R-chemotherapy

PRIMA study

1019 patients randomized after initial treatment with RCHOP, RCVP, or RFND

Rituximab once every 2 months x 2 years		Observation
75%	3 year progression free survival	57%
39%	Infections	24%

Follicular Lymphoma Case 2

- 46 female presented in 2012 with cervical lymphadenopathy of 3 months duration. No fever, B symptoms. Otherwise asymtomatic
- Hemoglobin 13; LDH 180
- CT C/A/P neck, upper abdominal lymphadenopathy (max size 3 cm)
- Bone marrow biopsy (10% involvement by FL)

Follicular Lymphoma Case 2

FLIPI score (Follicular Lymphoma International Prognostic Index)

Age > 60 (no)

LDH (lactate dehydrogenase) > upper limit of normal (no)

Hemoglobin > 12 (no)

Ann Arbor Stage III or IV (yes)

Number of involved areas > 4 (no)

FLIPI Low risk (1 risk factor) category

Follicular Lymphoma Case 2

- Management: Watchful waiting

  Rituximab single agent

  Rituximab with chemotherapy

- Options 1 and 2 discussed.

- Sought 2nd opinion. Discussed 1,2 and 3

- Patient elected to do single agent rituximab

Follicular Lymphoma Case 2

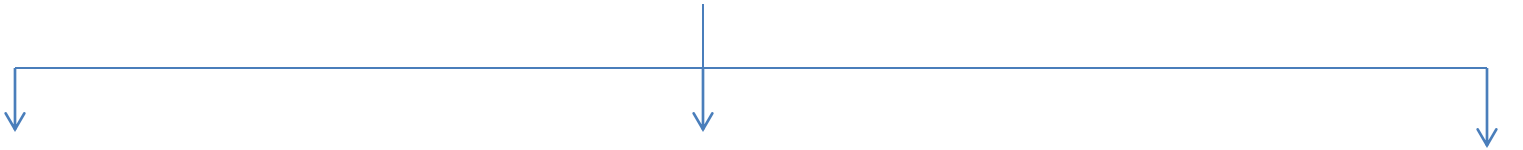
- She received weekly rituximab x 4
- Lymph nodes resolved clinically and on imaging
- Continues to do well.
- Follows up every 4 months for history and physical and blood count

Discussion points

- Watch and wait versus treat?
- Maintenance rituximab after single agent rituximab

UK Study

379 patients low tumor burden FL in UK, Aus, NZ, Poland and Turkey



Watch & Wait	Rituximab weekly x 4	Rituximab weekly x 4 every 2mo x 12
	ARM CLOSED	

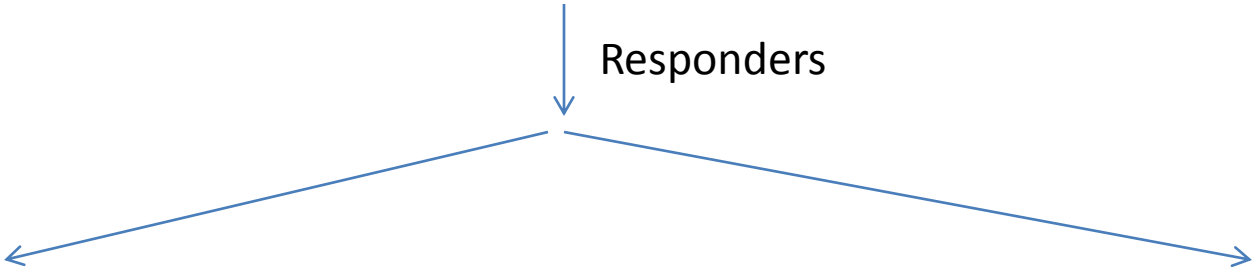
Number not needing treatment at 3 yrs

46%

88%

RESORT Study (E4402)

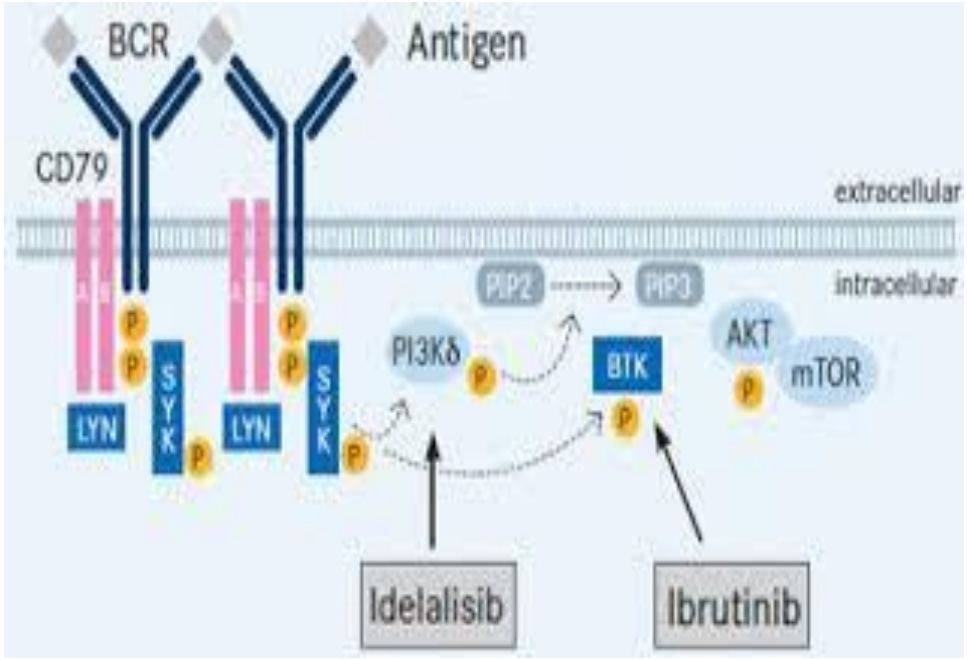
Previously untreated low tumor burden FL received rituximab x 4



Rituximab re-treatment		Rituximab maintenance
Treatment at time of progression		Once every 3 months till progression
3.9 yrs	Time to treatment failure	4.3 yrs
84%	3 year freedom from cytotoxic therapy	95%
4	Median number of rituximab doses	18

Relapsed/ Refractory Disease

- Idelasib (Zydelig) a PI3Kδ inhibitor most recent drug to be approved
- PI3Kδ highly expressed in hematologic cell surface and is important in conducting signals that allow normal cell development and function.
- Hyperactive in B cell cancers making it an attractive target


BCR
Antigen
CD79
extracellular
intracellular
PIP2
PIP3
PI3Kδ
BTK
AKT
mTOR
LYN
SYK
LYN
SYK
Idelalisib
Ibrutinib

Relapsed/ Refractory Disease

- Study 101-09 included 125 patients with indolent lymphoma that were refractory to rituximab and chemotherapy
- Median number of previous regimens was 4
- Overall response rate 57% (6% complete response)
- Median time to response was 2 months and duration was 12.5 months
- Diarrhea (43%/13%), neutropenia (56%/27%), liver enzyme elevation (40%/10%),
- Pneumonia 10%

CALGB 50401

Phase 2 study of relapsed lymphoma more than 6 months after last rituximab treatment

94 patients

Lenalidomide		Lenalidomide + Rituximab
49%	Response Rate	75%
14 months	Progression free survival	24 months

GADOLIN

396 patients with rituximab refractory iNHL. Patients had received average of 2 prior therapies

Bendamustine		Bendamustine + obinutuzumab
63%	Response Rate	69%
14 mo	Progression free survival	29 mo
63%	≥ grade 3 adverse events	69%

Waldenstrom's Macroglobulinemia

- WM is an indolent B-cell lymphoma associated with clonal lymphoplasmacytic cells and monoclonal IgM secretion
- Current active drugs used in 1st line settings include cyclophosphamide, steroids, bortezomib, bendamustine, rituximab. Fludarabine that was used previously is not go-to drug anymore
- First line treatment is highly active with durable responses. However, relapses do occur and approach to treatment is on the lines of other iNHL
- Ibrutinib (BTK-bruton tyrosine kinase) inhibitor approved for CLL, relapsed MCL and relapsed Waldenstrom's Macroglobulinemia

Waldenstrom's Macroglobulinemia

- 63 patients with WM that received at least 1 prior treatment received ibrutinib at 420mg daily
- Overall response 90%; major response 73%
- At 2 years, 69% were estimated to be progression free and 90% expected to be alive
- Neutropenia and thrombocytopenia were main adverse effects

Hairy Cell Leukemia

- HCL is a chronic, indolent B-cell cancer characterized by low blood counts (and its complications) and enlarged spleen
- Treatment is initiated at onset of symptoms or when counts significantly low
- Purine analogues (cladribine and pentostatin) and used in first line setting. Appx 30-50% relapse and with retreatment (rituximab also used in retreatment setting) duration of response will shorten and/or bone marrow reserve declines due to stem-cell toxic nature of the above drugs
- BRAF V600E mutation is seen in almost 100% of HCL cases making drugs that target the above mutation potential treatment options

Vemurafinib in HCL

- Vemurafinib is an oral BRAF inhibitor
- Patients with relapsed/refractory HCL to purine analogues were treated with vemaurafinib 960mg twice a day
- 2 studies were conducted. One in Italy and other in US
- Overall response rates were 96% and 100% respectively
- Complete responses were 35% and 42% respectively
- Average relapse free time was 19 months for patients with CR and 6 months in patients with partial response.

- Thank you for your attention!
- Questions