Updates in Indolent Lymphoma

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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
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
  - 94% overall response rate
  - 40% complete response rate
  - 70 months progression free survival (months)
  - 0% alopecia when 3 or more cycles
  - 37% infections
  - 7% peripheral neuropathy
  - 30% hematologic toxicity
  - 6% mouth sores
  - 16% rash/skin reactions

- RCHOP
  - 94% overall response rate
  - 30% complete response rate
  - 31 months progression free survival (months)
  - 100% alopecia when 3 or more cycles
  - 60% infections
  - 29% peripheral neuropathy
  - 68% hematologic toxicity
  - 19% mouth sores
  - 9% rash/skin reactions
Role of bendamustine

BRIGHT Study

BR
- Response Rate: 97%
- Complete Response: 31%
- Alopecia: 4%
- Peripheral neuropathy: 12%
- Rash: 22%

RCHOP
- Response Rate: 92%
- Complete Response: 25%
- Alopecia: 50%/21%
- Peripheral neuropathy: 45%
- 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, fatigue, thrombosis)
- RELEVANCE: Ongoing phase 3 studies assessing R2 versus R-chemo (STAY TUNED!)
Rituximab maintenance after R-chemotheraphy

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 asymptomatic

• 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 2\textsuperscript{nd} 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

Responders

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
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

49% Response Rate

14 months Progression free survival

Lenalidomide + Rituximab

75% Response Rate

24 months Progression free survival
GADOLIN

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

Bendamustine

- 63% Response Rate
- 14 mo Progression free survival
- 63% ≥ grade 3 adverse events

Bendamustine + obinutuzumab

- 69% Response Rate
- 29 mo Progression free survival
- 69% ≥ grade 3 adverse events
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 vemurafinib 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