Waldenström's Macroglobulinemia and Amyloidosis

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DISCLOSURES

Off-Label Usage
  • None

Interests
  • Celgene
  • Neotope
  • Onyx Pharmaceuticals
MONOCLONAL GAMMOPATHIES
MAYO CLINIC

n=34,633

MGUS 59% (20,580)
Multiple myeloma 18% (6,112)
Amyloidosis (AL) 9% (3,185)
Lymphoproliferative 3% (1,089)
SMM 4% (1,300)
Solitary or extramedullary 2% (705)
Macro 2% (785)
Other 3% (877)

12:2:1
PATIENT 1

- ‘Atypical Myeloma’ $\lambda 0.8g/dL$
- Marrow 8% PC’s Hb 14.4,
- Unexplained fatigue, can’t climb stairs, stops to rest 50 yards
- Depression about early myeloma
- Clues: EKG: low voltage, pseudo infarct, Neck veins distended due to restricted filling
Patient EKG-Normal Coronary Angio
Anterior Infarction ("Pseudoinfarct")
BONE MARROW BIOPSY CONGO RED X1000
PATIENT 2

- 79 yo W M DOE 1 yr, LE edema
- Echo concentric LVH, EKG Anterior infarct
- Cath negative, normal coronaries
- Referred to Mayo for non cardiac dyspnea
Urine Total Protein
0.22g/day

FLC λ 180 mg/L; κ 9 mg/L
FLC ratio 0.05
PATIENT 2

- Mayo Echo: Heart Walls & Valves Thickened Restrictive diastolic filling (stiff heart)-HFpEF
- Hypertrophy reinterpreted as infiltration
- Fat Aspirate +
- Began Protocol Chemotherapy
2007 Internist finds cholesterol 350 (last year 228), begins statin 18 mos. no reduction routine u/a proteinuria

Nephrologist : nil disease or MPGN

Prednisone 1 mg/kg 2 mos no benefit

Renal Biopsy

No screen for a light chain done
Renal Biopsy Demonstrating “Hyaline” Eosinophillic Amorphous Deposits
71 yo M progressive sensory motor PN
- Neurologist finds 1.1 g/dL G\(\lambda\)
- Diagnosis MGUS-Neuropathy (CIDP like)
- Plasma Exchange- IvIg tried over 8 months
- Given azathioprine & prednisone
- Progress & referred
- Sural n biopsy + amyloid
PT 5 HEALTHY 40 YO M

- Headaches acne VMR
- Incidental IgM\(\kappa\) protein
- Diagnosed MGUS
- Followed annually
- M protein does not change
FALLING SERUM ALBUMIN 4.0 TO 2.2
URINARY PROTEIN LOSS TO 10G/D

3% of MGUS will develop amyloidosis
CONSIDER AL IN:

- Non-diabetic nephrotic syndrome - check for light chains
- Non-ischemic cardiomyopathy with an echocardiogram showing “LVH” - check for light chains
- Hepatomegaly or alkaline phosphatase elevation without imaging abnormality - check for light chains
- Peripheral neuropathy with MGUS or CIDP with autonomic features
- Atypical myeloma monoclonal light chains urine and modest marrow plasmacytosis.
- Immunofixation serum and urine and serum-free light chain assay
- If Assay is negative
  - It's not amyloidosis
  - It's localized amyloidosis and not systemic
  - If it's systemic it could be senile or familial
Sensitivity 75%
AMYLOID TYPING

- Verify that the amyloidosis is light chain with your pathologist
  - 3-5% of elderly patients with localized, familial, senile & secondary amyloidosis will have an incidental unrelated MGUS
- Classic sites for localized amyloidosis are bladder larynx & skin
### Distribution of Amyloid types

<table>
<thead>
<tr>
<th>Amyloid Subtype</th>
<th>Number (%) of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>2553 (61.68)</td>
</tr>
<tr>
<td>ATTR</td>
<td>1015 (24.52)</td>
</tr>
<tr>
<td>AA</td>
<td>151 (3.65)</td>
</tr>
<tr>
<td>ALect2</td>
<td>148 (3.58)</td>
</tr>
<tr>
<td>Alns</td>
<td>48 (1.09)</td>
</tr>
<tr>
<td>Keratin*</td>
<td>36 (0.87)</td>
</tr>
<tr>
<td>AApoA1</td>
<td>30 (0.72)</td>
</tr>
<tr>
<td>AH</td>
<td>27 (0.65)</td>
</tr>
<tr>
<td>AFib</td>
<td>26 (0.63)</td>
</tr>
<tr>
<td>TGFB1-IP*</td>
<td>22 (0.53)</td>
</tr>
<tr>
<td>AApoA4</td>
<td>20 (0.48)</td>
</tr>
<tr>
<td>AANF</td>
<td>14 (0.34)</td>
</tr>
<tr>
<td>Ab2M</td>
<td>12 (0.29)</td>
</tr>
<tr>
<td>AGel</td>
<td>12 (0.29)</td>
</tr>
<tr>
<td>ASem1</td>
<td>12 (0.29)</td>
</tr>
<tr>
<td>APro</td>
<td>7 (0.17)</td>
</tr>
<tr>
<td>ALys</td>
<td>3 (0.07)</td>
</tr>
<tr>
<td>ACal</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>Enfuvirtide*</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>AIAPP</td>
<td>2 (0.05)</td>
</tr>
</tbody>
</table>

28% of amyloid biopsies are not AL and Chemotherapy contraindicated.
Several areas are traced in the computer screen, microdissected.
κ-light chain V-III

Identifies amyloid in formalin fixed tissue as immunoglobulin - AL

Now done routinely on all fat aspirates and bone marrow biopsies at Mayo

Laboratory Investigation (2008) 88, 1024–1037
(A) Kaplan-Meier curves for overall survival (OS) from diagnosis among the subgroup of 583 patients based on the new staging system.

Patients were assigned a score of 1 for each of FLC-diff $\geq 18$ mg/dL, cTnT $\geq 0.025$ ng/mL, and NT-ProBNP $\geq 1,800$ pg/mL, creating stages I to IV with scores of 0 to 3 points, respectively.

OS from stem-cell transplantation among 303 patients based on the new staging system

103 patients enrolled onto different trials

Kumar S et al. JCO 2012;30:989-995
©2012 by American Society of Clinical Oncology
In Amyloidosis a hematologic response translates into improved survival. Goal is suppression of light chain synthesis.
Surviving months

<table>
<thead>
<tr>
<th>Group</th>
<th>Surviving Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>1</td>
<td>114.8</td>
</tr>
<tr>
<td>2</td>
<td>64.9</td>
</tr>
<tr>
<td>3</td>
<td>29.5</td>
</tr>
</tbody>
</table>

N=410
BORTEZOMIB IS ACTIVE IN AL IN 2 DOSING SCHEDULES

• The hematologic response rate was 68.8% and 66.7% (37.5% and 24.2% complete responses), respectively;
• median time to first/best response was 2.1/3.2 and 0.7/1.2 months,
• One-year hematologic progression-free rates were 72.2% and 74.6%,
• 1-year survival rates were 93.8% and 84.0%, respectively

Bortezomib (1.5 mg/m² weekly), ctx (300 mg/m² po weekly) and dex (40 mg weekly)

17 patients received 2-6 cycles of CyBorD. Ten (58%) had symptomatic cardiac involvement and 14 (82%) had >1 organ involved. Resp occurred in 16 (94%), with 71% CR and 24% a PR.

Time to response was 2 mo. 3 patients not eligible for ASCT became eligible.

Blood. 2012 Feb 13. [Epub ahead of print]
RD AMYLOIDOSIS - SALVAGE

- AL refractory to both melphalan and bortezomib Rx with lenalidomide and dexamethasone
- 24 patients. 19 were also refractory to thal. Two died before evaluation of response, & 50% severe adverse events. Survival was significantly shorter in subjects with troponin I >0.1 ng/mL and in patients diagnosed <18 months before treatment initiation. HR was 41%; median OS 14 mo

POMALIDOMIDE

- Pom/dex combination in patients with previously treated AL
- 82% percent had cardiac involvement. Response rate was 48%, with a median time to response of 1.9 months. Organ improvement was documented in 5/33
- OS & PFS rates were 28 mo and 14 mo. The 1-year OS and PFS rates were 76% and 59%.

Blood First Edition Paper, prepublished online April 4, 2012;
Amyloidosis suspected
- Immunofixation of serum and urine
  - Free light-chain assay
    - Positive: Obtain fat and bone marrow specimens for Congo red staining
      - Positive: Is amyloid localized (not systemic), such as bladder, larynx?
        - Yes: Refer for local therapy
        - No: Could systemic amyloid be non-light chain? (transthyretin, fibrinogen, amyloid A β 2-microglobulin, etc)
          - Yes: Refer patient to specialty center
          - Uncertain: chemotherapy
          - No: chemotherapy
    - Negative: Light-chain amyloid unlikely. Consider other types of amyloidosis
      - Consider other types of amyloidosis
      - Organ biopsy if a high index of suspicion

Newly Diagnosed AL Amyloidosis

Transplant Eligible¹

- Mel 200 HSCT²,³

Transplant Ineligible¹

- Not wanting transplant
  - Mel-Dex or CyBoRd

Hematologic VGPR

- No Hematologic VGPR
  - Observation
  - < PR
    - More chemotherapy
  - ≥ PR
    - Low risk?⁵
      - Yes
      - No
  - ≥ PR

¹ Criteria for ASCT: Troponin T <0.06 and NT-proBNP <5000
² Induction therapy for 2-4 cycles if AL with >10%PC, CRAB present, or as clinically indicated
³ For age >70 or CrCl <30, use Mel 140 mg/m²
⁴ If hematologic parameter not decreased by >25% at 2 months, consider changing therapy
⁵ Mayo 2012 stage I (NT-pro-BNP <1800 ng/L, cardiac troponin T <0.025 mcg/L, and dFLC<18 mg/dL) or II (any 1 abnormal)
Treatment of AL – off study

Relapsed/ Refractory AL Amyloidosis

Not bortezomib refractory
- CyBorD or Vd

Not alkylator refractory
- Mel-Dex

Bortezomib refractory
- Len-Dex or Pom-Dex
WALDENSTRÖM'S CHARACTERISTICS

• Plasmacytic + lymphoplasmacytic lymphoma
• Post germinal center B cell
• Somatic hypermutation present
• CD19+ CD20+ CD79a+ CD138+
• CD10- CD23- CD5- (some macros may express CD5)
### MACROGLOBULINEMIA DEFINITIONS

<table>
<thead>
<tr>
<th></th>
<th>Monoclonal Serum IgM</th>
<th>Marrow Infiltration</th>
<th>Sx. Due to IgM Protein</th>
<th>Sx due to Tumor Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM Symptomatic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>WM Smoldering</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgM related disorder</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>MGUS</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abnormality</td>
<td>Prevalence (%)</td>
<td>Genes involved</td>
<td>Regular function</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>---------------</td>
<td>----------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td><strong>MYD88</strong></td>
<td>87-100</td>
<td><strong>MYD88</strong></td>
<td>Innate and adaptive immune response</td>
<td></td>
</tr>
<tr>
<td>−6q21</td>
<td>38-50</td>
<td><strong>PRDM1</strong></td>
<td>Suppression of cell proliferation</td>
<td></td>
</tr>
<tr>
<td>−6q23</td>
<td>38-50</td>
<td><strong>TNFAIP3</strong></td>
<td>Tumor suppressor gene. Negatively regulates the NF-κB pathway</td>
<td></td>
</tr>
<tr>
<td>+4</td>
<td>12-20</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+6p</td>
<td>17</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+18</td>
<td>17</td>
<td><strong>MALT1, BCL2</strong></td>
<td>Blocks the apoptotic pathway</td>
<td></td>
</tr>
<tr>
<td>+3</td>
<td>10</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Factors Associated with Prognosis in the IWMSS

- Age  >65
- Hemoglobin  <11.5 gr/dL
- Platelet count  <100k/ml
- B2-microglobulin  >3 mg/dL
- Monoclonal IgM concentration  >7 gr/dL

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Factors</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 or 1 (except age)</td>
<td>142.5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Age&gt;65 or 2</td>
<td>98.6</td>
</tr>
<tr>
<td>High</td>
<td>&gt;2</td>
<td>43.5</td>
</tr>
</tbody>
</table>

Table 2. Response Rates After Combined Fludarabine, Cyclophosphamide, and Rituximab in 43 Patients With Waldenstrom Macroglobulinemia Enrolled in the Current Study

<table>
<thead>
<tr>
<th>Response</th>
<th>End of Treatment</th>
<th>Best Response During Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>34 (79)</td>
<td>34 (79)</td>
</tr>
<tr>
<td>Major response</td>
<td>32 (74.4)</td>
<td>33 (76.7)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>5 (11.6)</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td>Very good partial remission</td>
<td>9 (20.9)</td>
<td>6 (13.9)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>18 (41.8)</td>
<td>19 (44.1)</td>
</tr>
<tr>
<td>Minor response</td>
<td>2 (4.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (9.3)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Progressive disease/failure</td>
<td>1/4 (11.6)</td>
<td>1/4 (11.6)</td>
</tr>
</tbody>
</table>

In 5 patients, an improved response was achieved during follow-up after a median of 6 months (range, 3-12 months). In 1 patient, a minor response converted to a PR, and 3 patients who were categorized with VGPRs achieved CR. Considering the best response, we observed a 76.7% major response rate (33 patients), including 18.6% CRs (8 patients), 13.9% VGPRs (6 patients), and 44.1% PRs. No statistical difference in terms of response was observed between pretreated and untreated patients, although, in naive patients, a trend was detected toward achieving a better quality of response (43% vs 14%; P = .086) (Table 3) 4.
BORTDR RESPONSE ASSESSMENT

- **N** = 23
- **Overall Responses**
  - CR: 3 (13%)
  - nCR: 2 (9%)
  - VGPR: 3 (10%)
  - PR: 11 (48%)
  - MR: 3 (13%)
- Median time to response 1.4 months
- With a median follow-up of 22.8 months (range, 3.3 to 33.2 months), all patients are alive
- 18/23 patients remain free of disease progression

41 patients with WM, of whom 22 received bendamustine and rituximab and 19 received R-CHOP.

In both groups, the response rate was 95%.

The median PFS for R-CHOP was 36 mo Vs not reached with bendamustine and rituximab ($P<.0001$). At analysis, 4 relapses (18%) in the bendamustine and R group & 11 relapses (58%) in the R-CHOP group.

*Lancet.* 2013 Feb 19
Figure 3  Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D)  B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Gr?nhagen, Christoph Losem, ...

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial
The Lancet null 2013 null

http://dx.doi.org/10.1016/S0140-6736(12)61763-2
PEARLS

- Carfilzomib and Ibrutinib both have clear activity in WM integration into clinic in evolution
- Everolimus is active
- Bortezomib neurotoxicity rates are higher than seen in myeloma patients
- Fludarabine & RCD remain good alternatives
Consensus for Newly Diagnosed Waldenström’s Macroglobulinemia

- IgM MGUS (<10% lymphoplasmacytic infiltration)
- Asymptomatic/smoldering Waldenström’s
- Hemoglobin ≥11 g/dL
- Platelets ≥120 x 10⁹/L

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 x 10⁹/L
- Neuropathy (IgM-related)
- WM-associated hemolytic anemia

- Bulky Disease
- Profound cytopenias –
  - Hemoglobin ≤10 g/dL
  - Platelets <100 x10⁹/L
- Constitutional symptoms
- Hyperviscosity symptoms

↓ Hyperviscosity

Yes
↓ Plasmapheresis
No

Observation

Single Agent Rituximab*
(1 cycle; no maintenance therapy)
*plasmapheresis if hyperviscosity develops with treatment

Dexamethasone + Rituximab + Cyclophosphamide (DRC)*

Ansell SM. Mayo Clinic Proc 2010;85:824-833; *Bendamustine + rituximab is an alternative

v3 Revised May 2013