Myeloma 101 Updates and Pain Management Perspectives

Brian GM Durie, MD
Thursday, November 19\textsuperscript{th}, 2015
1. What to expect from ASH 2015– a preview
   • Research
   • “Clinical pearls”: New 101 Tips

2. Summary of pain management in myeloma
1. Minimal residual disease (MRD)
2. Molecular tests/subclones
3. Triple therapy ± transplant
4. Role of transplant
5. Carfilzomib (Kyprolis®)
6. Ixazomib (Ixaz)
7. Anti-CD38 MoAbs [DAR/SAR/MOR 202]
8. Elotuzumab (Elo)
9. Checkpoint inhibitors
10. Clinical “pearls”

Plus

• Path to a CURE
• Education sessions
• Beutler lecture (proteasome inhibitors)
1. Minimal Residual Disease

… over 20 abstracts

• Depth of response linked to better outcomes
• Different tests feasible: NGS/NGF/Imaging
• Multiple myeloma subclones
• Blood tests
• New methods
• New trials

Abstracts

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MRD monitoring in MM using NGF: ultra-sensitivity

Next-generation flow (NGF)

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<th>-</th>
<th>+</th>
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<td>9/14</td>
<td>2/14</td>
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<td>(64%)</td>
<td>(14%)*</td>
<td>(78%)</td>
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<td>0/14</td>
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<td>(0%)</td>
<td>(22%)</td>
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<td>(64%)</td>
<td>(36%)</td>
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NGS was applicable in 14/16 (88%) of MM cases
## New Criteria for MRD

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<th>MRD-negative by Next-generation flow (NGF)</th>
<th>Conventional CR PLUS</th>
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<td>NGF</td>
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<td>Minimum sensitivity @ $10^{-5}$</td>
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<td>Current sensitivity @ $10^{-6}$</td>
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<table>
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<th>MRD-negative by Next-generation sequencing (NGS)</th>
<th>Conventional CR +PLUS</th>
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<th>Imaging plus cellular MRD-negative category</th>
<th>MRD negative as defined above (NGF or NGS) PLUS</th>
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<td>Disappearance of every area of increased tracer uptake found at baseline by PET/CT</td>
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MRD monitoring in multiple myeloma using NGS

1. Extraction and quantification of gDNA (qPCR)
2. VDJ, DJ, KDEL etc. PCR amplification with Biomed 2 primers
3. Ligation with barcodes
4. Sequencing, Ion Proton Platform

Martinez-Lopez J, et al.
Going beyond the CR criteria with MRD monitoring

- < 5% PCs in bone marrow
- Negative IFE of serum and urine
- Disappearance of soft tissue plasmacytomas

**Cellular clonality**
- Immunohistochemistry
- ASO-PCR
- Next Generation Sequencing (NGS)
- Next Generation Flow (NGF)

**Cellular production**
- sFLC
- Hevylite
- Sensitive M-spike measurement

**Cellular spread**
- PET/CT
- WB-MRI
Discrimination by Depth of MRD

- 
- 
- 

PFS

Negative @ $\leq 10^{-6}$

100%

1 year 3 years 5 years

$10^{-4}$

$10^{-5}$

Years Off Therapy

CURE
Categories of MRD Negative

- **MRD –**
- **No relapse**

**PFS**

1. Relapse on Rx
2. Relapse off Rx
3. Potential CURE
4. MGUS signature
5. Resistant myeloma

**Years of Rx**

- Years: 1, 3, 5
Steps to Assess and Treat MRD

If positive:
- Study Residual MRD
- Develop specific Rx
- Assess Relapse/Resistant Disease
  - Car/Rev/Pom/+ Elo or DARA
  - Alternate Rx

If negative:
- Monitor or Maintain
- MoAb Studies
- MRD Assessment

International Myeloma Foundation
2. Molecular Tests & Subclones

- DNA sequencing
- RNA sequencing
- Mutational analyses
- Sequential clonal evolution (branching or not)
- Search for “driver” mutations
- Bone marrow/Blood/EMD

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3. Triple Therapy ± Transplant

- VRd v Rd (SWOG S0777)
- VRD ± ASCT (IFM/DFCI Trial)
- VTd v VCd
- VMP
- Vd v CARd

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**SWOG S0777 Study Design**

**Eight 21-day Cycles of VRd**
- **Bortezomib (Velcade®) 1.3/mg² IV**
  - Days 1, 4, 8, and 11
- **Lenalidomide (Revlimid®) 25 mg/day PO**
  - Days 1-14
- **Dexamethasone 20 mg/day PO**
  - Days 1, 2, 4, 5, 8, 9, 11, 12

**Six 28-day Cycles of Rd**
- **Lenalidomide (Revlimid®) 25 mg/day PO**
  - Days 1-21
- **Dexamethasone 40 mg/day PO**
  - Days 1, 8, 15, 22

**Randomization**
- **N = 525**

**Stratification:**
- ISS (I, II, III)
- Intent to transplant @ progression (yes/no)
SWOG S0777 Study Design (continued)

VRd

Rd

After induction

Rd Maintenance Until PD, Toxicity or Withdrawal

- Lenalidomide (Revlimid®)
  25 mg PO days 1-21
- Dexamethasone
  40 mg PO days 1, 8, 15, 22

- All patients received Aspirin 325 mg/day
- VRd patients received HSV prophylaxis
Progression-Free Survival By Assigned Treatment Arm

- **VRd**: 137/242, Median 43 (39, 52)
- **Rd**: 166/229, Median 30 (25, 39)

Months from Registration
4. Role of Transplant

• Role of autotransplant
• Role of consolidation
• Salvage autotransplant
• Allo transplant

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5. Carfilzomib (Kyprolis®) Results

- CAR d v VEL d (Endeavor Trial)
- 1/week CAR
- CAR dose escalation
- CAR Cd/CAR MP
- Other CAR combos: Rd/Selinexor/Array

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6. Ixazomib

- Ixaz Rd v Rd: pivotal trial [Tourmaline: MM01]
- Ixaz + Cd
- Ixaz + Pom d
- Ixaz maintenance (safety)
- Ixaz + panobinostat
- Ixaz dose escalation (4 mg vs 5 mg)
- Renal hepatic corrections: 3 mg dose

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Specific Targets for New Therapies

**Antigens**
- CD 28
- CD 117
- CD 45
- CD 33
- CD 20
- CD 19
- CD 56
- CD 138
- CD 319 (SLAM F7)
- CD 38

**Molecular**
- BRAF
- KRAS
- NRAS
- CCND1
- DIS3
- HOX A9
- NFKB

Hundreds of mutations, SNPs, and pathways
Antigen/Receptor Targets

Multiple Targets

- **NK Cell**: KIR, CD 16, SLAM F7
- **CAR T cell**: CD 19
- **T Cell**: PD-1 checkpoint inhibitor
- **VSV**: Measles

International Myeloma Foundation
7. Anti-CD38 MoAbs

- Daratumumab approved in relapse/refractory setting on November 16th!
- Single agent/combo results presented at ASH
- SAR compound and MOR 202 data also presented

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US “CURE” Trial: ASCENT
Aggressive Smoldering Cure Evaluating Novel Rx Transplant

HR SMM

KRd + DARA x 4 cycles

ASCT MEL 200

KRd + DARA x 4 cycles

KRd + DARA x 4 cycles

KR – DARA x 1 year
8. Elotuzumab

- Eloquent-2: Rd ± Elo
- Elo + Vd
9. Checkpoint Inhibitors

- Anti-PD1 (Pembrolizumab) + Rd [Keynote-023]
- Pembrolizumab + Pomd

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10. Clinical “Pearls”

- Doxycycline for Amyloid Rx #732
- PET/CT for monitoring #395
- WB DWI MRI #1758 + Terpos DW MRI #4178
- Consolidation important #396
- DEX dose adjustment OK #1839
- Agent Orange exposure a poor risk factor #4194
- Statin use (Lipitor®) reduces risk of myeloma #4198
- Risk of Velcade® neuropathy: calcium and hemoglobin #4233
- Racial disparities: impact of biology and socioeconomics #633, #1767 and #4508
- RVd-Lite #4217
- V Cardo (v Len) #3046
- UPEP MGUS/SMM #2965
- ISS-R Validation #3045
Pain in Myeloma

• **Bone**
  • Active disease
  • Fracture
  • Nerve pressure
  • Spinal cord compression

• **Neuropathy**
  • Bortezomib (Velcade)
  • Ixazomib
  • Other

• **Infection**
  • Dental
  • Sinus
  • GI/Gallbladder
  • Other
Treatment for Pain

Treat Cause
- Myeloma
- Reduce/stop drug
- Infection

Treat Residual Pain
- Surgery
- Radiation
- Vertobro/Kyphoplasty
- Bisphosonates
- Nerve blocks
- Pain therapy
Drug Therapy for Pain*

- Morphine & derivatives (oxycodone…)
- “Opioids”
  - Ultram® (Tramadol)
  - Nucynta® (Tapentadol)
- Cymbalta (Duloxetine): ASCO: Level A evidence
- Anti-inflammatory
  - Steroids (dex/prednisone)
  - NSAIDs (Aleve®; Advil®)
- Topical
  - Lidocaine patch (5%)
  - Gabapentin (6%)
  - Menthol (1%)
  - Baclofen/amitriptyline/ketamine gel

*Reference: Symposium on Pain Management
Mayo Clinic Proceedings October 2015
Other Options for Pain

• Supplement “cocktail”
• Nerve stimulator (peripheral/central)
• Integrative: music/massage/healing touch
• Accupressure or acupuncture
• Specialized nerve blocks
Bottom Lines

• Lots of new information from ASH

• Myeloma pain IS usually manageable!