Combined Treatments and Clinical Trials for Better Outcomes in Multiple Myeloma

AZMNN Patient Conference

March 23, 2013

Scottsdale, Arizona
Rochester, Minnesota
Jacksonville, Florida

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Objectives

1. Introduce the subject of clinical trials
2. Describe the types and “phases” of clinical trials
3. Discuss the importance of clinical trials in the care of all cancer patients, especially in myeloma and their impact on survival
4. Highlight current clinical trials available at Mayo Clinic in Arizona
Clinical Trials

Remember some of the important principles of clinical trials:

• The drive of research has brought us to where we are

• No one is expected to be a “guinea pig”

• Research is under very tight supervision and standards

• Open, clear communication between the physician and the patient is fundamental
Clinical Trials – Why Me??

- Every patient is unique and must be viewed that way

- Benefits of trials are numerous and include:
  - Early access to “new” therapy
  - Delay use of standard therapy
  - Contribution to myeloma world – present and future
  - Financial access to certain agents

- Must be balanced with potential risks
  - “toxicity” of side effects
  - Possibility of lack of efficacy
Clinical Trials – Categories in MM

- Upfront therapy
- Relapsed therapy
- Supportive Care
- Transplant related trials
  - Conditioning, Consolidation, Maintenance

Agents used in combination

Single agent trials
Importance of Research

• From “Bench” to “Bedside”

• Better understanding of the disease allows for better drugs
  • Targets to treat
  • Interaction with other aspects of bone marrow (microenvironment)

• Has already proven impact on better survival…
OS From Time of Diagnosis in 6-yr Intervals Based on Date of Diagnosis

Kumar SK et al. Blood. 2008;111:2516
Multiple Myeloma 1971-2006
n=2,981

Survival, med
44.8 mo

Survival, med
29.9 mo

P<0.001

Diagnosis during/before 1996

Diagnosis after 1996

Multiple Myeloma Mayo Patients

S. Kumar, 2012

P < 0.0001
Treatment sequence

Front line treatment
- Induction
- Consolidation

Maintenance
- Post consolidation

Relapsed
- Nothing
- Thalidomide?
- Bortezomib?
- Lenalidomide?
- Bortezomib
- Lenalidomide
- Thalidomide
- Carfilzomib
- Pomalidomide
- Elotuzumab
- HDAC
- Bendamustine

New:
- Thal/Dex
  - VD
  - Rev/Dex
  - CyBorD
  - VTD
  - VRD
- SCT
- VD/VRD

Old:
- VAD
- DEX
- SCT
- Nothing
- Prednisone
- Thalidomide
- Few options
Types of Trials

• Phase 1: designed to test the safety of a drug (possibly efficacy)
• Phase 2: test efficacy of established drug
• Phase 3: test the agent in direct comparison with the current standard of care
Clinical Trials in the Treatment of Myeloma

**Phase I**
Tests safety

**Phase II**
Tests how well treatment works

**Phase III**
Compares new treatment to standard treatment
Even Before Phase I

- Most agents are tested in lab models
  - Various “myeloma cell lines” = in vitro
- Next step is animal model
  - We are more like mice than you think!!
- Earliest study in phase I is called “First in Human”
  - Often uses extremely low dose of drug to ensure safety
In Vitro Activity
Murine Activity
Phase 2

- This is the lion share of clinical trials
- Some are very small, but others large
  - Single center to multi-center
- Safe drugs (from Phase 1), prove their efficacy in Phase 2
Phase 3

• The true Gold Standard clinical trial
• Randomized and compared to standard of care
• Usually required to result in FDA approval
Myeloma at Mayo

• 5 Clinical Physicians
  • Rafael Fonseca
  • Keith Stewart
  • Leif Bergsagel
  • Joseph Mikhael
  • Craig Reeder

• 3 Labs
  • Fonseca – 7
  • Bergsagel - 6
  • Stewart - 5
Myeloma at Mayo

• Angela Mayo – Physician Assistant
• Tissue Bank – Dr. Esteban Braggio and Greg Ahmann
• Clinical Trial coordinators (6)
• Phase 1 program
• 3 Nurse Coordinators (Jacy, Joyce, Jennifer)
• Other allied health – secretaries, social workers, technicians...
Trials at Mayo Clinic Arizona 2007-2013

• Summary
  • 33 Myeloma Trials
    • 15 initiated by Mayo
  • Across spectrum
    • Phase 1, 2, 3
    • Pre/transplant/post
    • Young and old
  • Over 300 patients enrolled
Highlights of Major Trials

• Pomalidomide
  • 112 patients (!!!)
  • 27 patients in first 3 weeks of enrolment
  • Overall Mayo has treated more patients (450) then the rest of North America combined
  • Major contribution to its approval by FDA in February 2013
Highlights of Major Trials

• Carfilzomib
  • Several trials (newly diagnosed and relapsed)
  • Keith Stewart PI of Phase 3 Carfilzomib-Lenalidomide-Dex vs Lenalidomide-Dex (ASPIRE)
  • 003 and 004 studies that led to approval in July 2012
  • CYCLONE and NCCN recommendations last week
Clinical Trials

• Information available at:  
  www.clinicaltrials.gov

• Currently 1573 listed under myeloma!  
  • 482 still accruing

• 14 open clinical trials at Mayo Clinic Arizona
IMF Website for clinical trials


- Also note the Clinical Trial “Fact Sheets”
Clinical Trials with Current Drugs

- Often trials will explore combinations of agents already in use
  - Which combination is best (safe and efficacious)?

- Several open now combining:
  - Dexamethasone
  - Cyclophosphamide (cytoxan)
  - Thalidomide
  - Bortezomib (Velcade)
  - Lenalidomide (Revlimid)
  - Carfilzomib (Kyprolis)
Clinical Trials

Key Agents:

• Pomalidomide – “new” version of lenalidomide (revlimid)
  • Less neuropathy than thalidomide
  • Less “myelosuppression” (low blood counts) than lenalidomide
  • Phase 1 trials complete
  • Many phase 2 trials ongoing
  • Combination studies underway
  • FDA approved February 2012!
Clinical Trials

- Carfilzomib – “new” version of bortezomib (=velcade) ie. Proteasome inhibitor
  - IV drug given twice a week
  - Minimal neuropathy
  - Infusional issues +/- cardiac

- FDA approved July 2012 – 3 conditions
  - Previous bortezomib
  - Previous IMiD (thalidomide or lenalidomide)
  - Currently relapsing on therapy or within 60 days
Open Trials for Newly Diagnosed

- MC0982 A Phase I/II Trial of Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone (CYCLONE) in Patients with Newly Diagnosed Active Multiple Myeloma
Open Relapsed Trials at Mayo

1. **PrE1003** A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function

2. **MFG4809g** An Open-Label, Multicenter, Phase I Trial of the Safety and Pharmacokinetics of Escalating Doses of MFGR1877S in Patients with Relapsed or Refractory t(4;14)-Positive Multiple Myeloma

3. **MC1181** Phase 2 Trial of MLN9708 in Patients with Relapsed Multiple Myeloma Not Refractory to Bortezomib

4. **MC1082** A Phase I/II Trial of Pomalidomide, Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma
5. PKB115125 A Phase Ib Study of Oral AKT Inhibitor GSK 2110183 Administered with Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

6. TED10893 A Phase I Dose Escalation Safety and Pharmacokinetic Study of Multiple Intravenous Administrations of a Humanized Monoclonal Antibody (SAR650984) Against CD38 in Patients with Selected CD38+ Hematological Malignancies

7. MC088A Phase I/II Study of Combination of Aurora Kinase Inhibitor MLN8237 and Bortezomib in Relapsed or Refractory Multiple Myeloma

8. MC1182 Phase II Trial of nab-paclitaxel (Abraxane) in Patients With Relapsed or Refractory Multiple Myeloma

Others coming soon – Abraxane, Oprozomib, CRM1 Inhibitor, ABT101 and many others…
Results From the Phase II Dose Expansion of Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone (CYCLONE) in Patients with Newly Diagnosed Multiple Myeloma


Scottsdale, Arizona  Rochester, Minnesota  Jacksonville, Florida
Newly Diagnosed: CYCLONE Phase II

- Carfilzomib
- Cyclophosphamide
- Thalidomide
- Dexamethasone

Response
PFS
Toxicity
Stem cell harvest
Results Levels 0 and 1 – Response n=27

- Overall Response 96%

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<th>Count</th>
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<tr>
<td>CR</td>
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<tr>
<td>VGPR</td>
<td>13</td>
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<td>PR</td>
<td>6</td>
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<td>MR</td>
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≥ VGPR 74%
Response by Cycle

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<tr>
<th>ORR</th>
<th>81%</th>
<th>93%</th>
<th>96%</th>
<th>96%</th>
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</table>

![Bar chart showing response rates by cycle](chart.png)
Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide

**Thalidomide**
100-200 mg/d
Neuropathy
Constipation
Sedation
DVT

**Lenalidomide**
15-25 mg/d
Myelosuppression
Skin rash
DVT

**Pomalidomide**
1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively
<table>
<thead>
<tr>
<th>Patient population</th>
<th>N</th>
<th>Regimen/dose</th>
<th>ORR</th>
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<tbody>
<tr>
<td><strong>Phase 1 Pomalidomide trials</strong></td>
<td></td>
<td>Por bored escalation</td>
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<tr>
<td>Schey</td>
<td>24</td>
<td>MTD 2mg 28/28</td>
<td>54%</td>
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<tr>
<td>Streetly</td>
<td>20</td>
<td>Pom +/- dex</td>
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<td>Pom +/- dex</td>
<td>25%</td>
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<tr>
<td><strong>Phase 2 Pomalidomide trials</strong></td>
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<td>Por bored 4 mg 21/28</td>
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<tr>
<td>Richardson</td>
<td>120</td>
<td>Pom +/- dex, 4 mg, 21/28</td>
<td>25%</td>
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<tr>
<td>Lacy</td>
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<td>63%</td>
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<td>47%</td>
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<tr>
<td>Leleu</td>
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<td>Pom/dex 4 mg, 21/28</td>
<td>30%</td>
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<td>Clom postponed, 4 mg, 21/28</td>
<td>60%</td>
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Lacy Blood 2012, 120(21): abstr 201
Single-Agent Activity of 39 Drugs Tested in Multiple Myeloma

≥PR (%)
Novel Agents

- “newer” versions of current drugs
  - Pomalidomide
  - Carlfizomib
  - Newer proteasome inhibitors (oprozomib, MLN 9708, marizonib)

- Novel agents
  - Bendamustine
  - Perifosine
  - Vorinostat
  - LBH589
  - RAD001
  - SGN 40
  - Obatoclax
  - HGF inhibitors
  - BHQ
  - AUY922
  - Monoclonal antibodies (esp CD38)
  - Dasatinib
  - Vaccines
  - cdk Inhibitor SCH 727965
  - MLN8237 (Aurora A Kinase Inhibitor)
  - TAK-901
Combinations for Induction in Myeloma

![Graph showing percent response for different induction regimens (VAD, TD, RD, PAD, VTD, RVD, CVRD, CyBorD, CarRD*) with ORR, VGPR, and CR/nCR categories.](image)
mSMART

*Mayo Stratification for Myeloma And Risk-adapted Therapy*

Newly Diagnosed Myeloma

*Website: www.msmart.org*
### mSMART 2.0: Classification of Active MM

<table>
<thead>
<tr>
<th>High-Risk</th>
<th>Intermediate-Risk*</th>
<th>Standard-Risk*†</th>
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<tbody>
<tr>
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<td><strong>FISH</strong></td>
<td>All others including:</td>
</tr>
<tr>
<td>Del 17p</td>
<td>t(4;14)‡</td>
<td>Hyperdiploid</td>
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<tr>
<td>t(14;16)</td>
<td></td>
<td>t(11;14)**</td>
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<td>t(14;20)</td>
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<td>t(6;14)</td>
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<td><strong>GEP</strong></td>
<td><strong>Cytogenetic</strong></td>
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<td>High risk signature</td>
<td>Deletion 13 or hypodiploidy</td>
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<td><strong>PCLI ≥3%</strong></td>
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</tbody>
</table>

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Mikhael et al Mayo Clinic Proceedings April 2013
mSMART 2.0: Classification of Active MM

High-Risk 20%
- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

Intermediate-Risk 20%
- FISH
  - t(4;14)*
- Cytogenetic Deletion 13 or hypodiploidy
- PCLI ≥3%

Standard-Risk 60%
- All others including:
  - Hyperdiploid
  - t(11;14)
  - t(6;14)

3 years                      4-5 years                         8-10 years
mSMART – Off-Study

Transplant Eligible

**High Risk**
- VRD x 4
- ASCT, especially if not in CR
- VRD maintenance for minimum of 1 year

**Intermediate Risk**
- Induction with CyBorD
- Autologous stem cell transplant (ASCT)
- Bortezomib based consolidation for minimum of 1 year

**Standard Risk**
- 4 cycles of Rd or CyBorD
- Collect Stem Cells
- Autologous stem cell transplant (ASCT)
- Continue Rd
- Consider Lenalidomide maintenance*

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*Mikael et al Mayo Clinic Proceedings April 2013*
mSMART – Off-Study

Transplant Ineligible

High Risk

Intermediate Risk

MP + weekly Bortezomib**
or weekly CyBorD

Bortezomib maintenance

Standard Risk*

Rd\textsubscript{b,c}

Observation

Mikhael et al Mayo Clinic Proceedings April 2013
Conclusions

- Clinical trials are a critical part of advancing care in multiple myeloma
- There is a spectrum of trials from Phase 1 to Phase 3
- Selecting a trial is dependent on many patient and disease factors and must be discussed openly
- There are many new agents that provide great promise for patients with multiple myeloma