Mayo Clinic Myeloma Amyloidosis Dysproteinemia Group

Scottsdale, Arizona  Rochester, Minnesota  Jacksonville, Florida
Vision Statement

To Advance Individualized Care, Have a Global Impact, and Cure Myeloma and Related Disorders
Strength of Our Practice
Mayo Clinic 1960-2014

n=50,869

MGUS
57% (28,962)

Lymphoproliferative
3% (1,478)

AL amyloidosis
9.5% (4,801)

Multiple myeloma
17.5% (9,034)

SMM 4% (1,972)

Solitary or extramedullary
2% (913)

Macro
2.5% (1,397)

Other
4.5% (2,312)
Strengths

- Largest Myeloma and Related Disorders Groups in the World
- Multidisciplinary Group
  - Hematologists:
    - 20 at Mayo Clinic, Rochester, MN
    - 6 at Mayo Clinic Arizona
    - 4 at Mayo Clinic Florida
    - 14 hematologists are at Professor Level
  - Specialists in Divisions other than Hem/Onc:
    - 7 across the 3 sites
- Complete Integration across the 3 Mayo Clinic sites
- Myeloma SPORE (PI: Leif Bergsagel)
Strengths

• International Leadership in research, education, and practice
  • Molecular Classification of MGUS, SMM, and Myeloma
  • Risk-adapted therapy of Myeloma and Related Disorders
  • Epidemiology of Plasma Cell Disorders
  • Related Plasma Cell Disorders
    • MGRS
    • Amyloidosis
    • POEMS
    • Castleman’s disease
    • WM
• Mayo Led Clinical Trials
• Leadership in ECOG
• Extensive Clinical and Laboratory Databases
Unique Programs

- Epidemiology, Biomarkers (Rajkumar, Kyle, Kumar, Dispenzieri)
- Virotherapy (Russell, Dingli, Peng)
- Center for Individualized Medicine (Stewart)
- Vaccine and Adoptive Cell Therapy (Lin)
- Novel Imaging for Myeloma (Drake)
- Novel Laboratory Evaluation (Ketterling, Morice)
- Mass Spec (Murray, Bergen, Barnidge, Kurtin)
- Genomics (Stewart, Bergsagel, Fonseca)
- Novel Therapeutics (Stewart, Bergsagel, Kumar)
- Immunotherapy (Lin, Chanan-Khan)
- Hematology-Oncology Outcomes Research-Oriented Group (Go, Hashmi)
International Leadership

• NCI Multiple Myeloma Steering Committee
  • Shaji Kumar, Chair; Vincent Rajkumar- member

• ECOG Myeloma Committee
  • Vincent Rajkumar, Chair

International Leadership

- International Myeloma Working Group (IMWG)
  - Vincent Rajkumar, co-chair
- International Myeloma Foundation (IMF)
  - Robert Kyle and Vincent Rajkumar, Board Members; Robert Kyle, Chair of the Scientific Advisory Board
- International Waldenström's Macroglobulinemia Foundation (IWMF)
  - Robert Kyle and Steve Ansell, Board of Trustees; Robert Kyle, chair, Scientific Advisory Committee
- International Society of Amyloidosis (ISA)
  - Angela Dispenzieri, President
- International Myeloma Society (IMS)
  - Angela Dispenzieri, Treasurer
- International Kidney and Monoclonal Gammopathy Research Group (IKMG)
  - Nelson Leung, President; Angela Dispenzieri, Treasurer
Clinical Trial Leadership

• Principal Investigator (PI) Role on many prominent National/International Phase III Trials
  • Pomalidomide trials (Martha Lacy)
  • E1A06: MPT vs MPR (Keith Stewart)
  • MM 020: Rd vs MPT (Angela Dispenzieri)
  • S0777 Rd vs VRd (Angela Dispenzieri)
  • ASPIRE Rd vs KRd (Keith Stewart)
  • E1A11: VRD vs KRd (Shaji Kumar)
  • Ixazomib Rd vs IRd (Vincent Rajkumar)
  • Ixazomib Phase III AL (Angela Dispenzieri)
  • S1304: High/std. dose carfilzomib (Sikander Ailawadhi)
  • S1211: RVd vs RVd-Elo (Sikander Ailawadhi)
Publications

- ~80-100 per year excluding abstracts and book chapters
Education

- [http://www.msmart.org](http://www.msmart.org) Practice Guidelines
- [www.twitter.com/mayomyeloma](http://www.twitter.com/mayomyeloma)
- Myeloma Fellowship
- Kurtz Myeloma Research Fellowship
- Myeloma Book - Fully Mayo authored (Springer, 2013)
- Amyloidosis Book (Springer, 2010)
- UpToDate (All chapters related to myeloma and related disorders)
- Wintrobe Clinical Hematology
MGUS and SMM
# Developed Definition and Classification of MGUS, SMM, MM

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
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<tbody>
<tr>
<td>Bone Marrow/ M Protein</td>
<td>&lt;10% plasma cells <strong>AND</strong> &lt;3gm/dL M protein</td>
<td>10-60% plasma cells <strong>OR</strong> ≥3 gm/dL M protein</td>
<td>≥10% plasma cells</td>
</tr>
<tr>
<td>Clinical Picture</td>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
<td>MDEs</td>
</tr>
<tr>
<td></td>
<td>No end-organ damage*</td>
<td>No MDEs</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>Observation only</td>
<td>Observation only</td>
<td>Therapy required</td>
</tr>
</tbody>
</table>

MDEs: Hypercalcemia, anemia, renal failure or lytic bone lesions attributable to plasma cell disorder; 
>=60% clonal PCs; >=100 FLC ratio; >1 focal lesion on MRI

Determined the Prevalence of MGUS in USA

- MGUS present in 3% of general population >50 years
- 1.7% in 50-59
- >5% in over 70
- Men > Women

Defined and Determined Prevalence of Light Chain MGUS

- LC-MGUS is present in 0.8% of general population ≥50 years.
Determined 2-fold Increased Prevalence of MGUS among African Americans in USA

n = 12,482

Prevalence of MGUS (%) vs Age in years

- Whites
- Blacks
- Mexican-Americans

Landgren O....Rajkumar SV. Leukemia 2014
Defined Risk of Progression of MGUS and SMM

Estimated MGUS Annual Health Care Costs in USA

Clinical prevalence (diagnosed cases) of monoclonal gammopathy of undetermined significance in the US: estimating the burden on health care

- About 540,000 individuals living with a diagnosis of MGUS
- At least $110 million annual cost to health care
Demonstrated MGUS always precedes MM

100% had preceding MGUS

Landgren, O……Rajkumar SV. Blood 2009;113:5412-5417
Developed Cytogenetic Classification of SMM

<table>
<thead>
<tr>
<th>High-Risk</th>
<th>High-Intermediate</th>
<th>Low-Intermediate</th>
<th>Low-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Del 17p&lt;br&gt;- t(4;14)&lt;br&gt;- Gain(1q)</td>
<td>- Trisomies</td>
<td>- All other</td>
<td>- No cytogenetic abnormalities</td>
</tr>
</tbody>
</table>

*Median TTP ~2 years<br>Median TTP ~3 years<br>Median TTP ~5 years<br>Median TTP ~10 years*

Myeloma Biology
Led Many Studies on Pathogenesis of MGUS and its progression to myeloma.


©2009 by American Association for Cancer Research
First determined two major subtypes of Myeloma Hyperdiploid and Non-Hyperdiploid

Gene expression

Fonseca Blood 102:25622003
Developed genetic classification of hyperdiploid myeloma

First to show inverse relationship between IgH Translocations and trisomies

First comprehensive genetic description of MGUS and AL; MGUS similar to MM and AL 50% t(11;14)


Developed Vk*MYC mouse model of Myeloma

Chesi et al. Cancer Cell 2008
Identified MYC rearrangements in ~50% of MM patients

Method | % MYC rearrangements
---|---
FISH | 15%
aCGH | 44%
Either | 49%

Condition | % MYC rearrangements
---|---
Untreated | 47%
Relapsed | 52%
t(11;14) | 25%
Hyperdiploid | 66%

Juxtaposition of super enhancers adjacent to MYC

1/3 Ig enhancers - distributed equally across genetic subtypes
2/3 non-Ig enhancers - more common in hyperdiploid

Affer et al, Leukemia 2014
Identified that mutations of NFkB are frequent in Myeloma
Described Clonal Tides in Myeloma

Healthcare Disparities in Myeloma

• First to show that Hispanics have the worst outcome of all racial/ethnic subgroups in myeloma.

• First to explore the benefit of NCI/NCCN centers on outcomes in myeloma:
  • Benefit of NCI centers within SEER registry seen only in Whites
  • Benefit of NCCN centers within SEER registry seen in Whites and African-Americans, not in other minorities.

Demonstrated Improved Survival in Myeloma

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma


This International Myeloma Working Group consensus updated the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be
Led Development of International Staging System for Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival in Months</th>
</tr>
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<tbody>
<tr>
<td>Stage I</td>
<td></td>
</tr>
<tr>
<td>$\beta 2M &lt; 3.5$ and albumin $\geq 3.5$</td>
<td>62</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
</tr>
<tr>
<td>Not meeting criteria for Stage I or III</td>
<td>44</td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
</tr>
<tr>
<td>$\beta 2M \geq 5.5$</td>
<td>29</td>
</tr>
</tbody>
</table>

Greipp PR. J Clin Oncol 2005;23:3412-3420
Developed Cytogenetic Classification of Myeloma

- **t(11;14) (CCND1)**
- **t(6;14) (CCND3)**
- **Trisomies**
- **t(4;14) (FGFR3/MMSET)**
- **t(14;16) (C-MAF)**
- **t(14;20) (MAF-B)**

~10% have both trisomies and IgH translocations

Developed Cytogenetic Myeloma Risk-Stratification

<table>
<thead>
<tr>
<th>Standard-Risk</th>
<th>Intermediate-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomies</td>
<td>t(4;14)</td>
<td>t(14;16)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Gain (1q)</td>
<td>t(14;20)</td>
</tr>
<tr>
<td>t(6;14)</td>
<td></td>
<td>Del 17p</td>
</tr>
</tbody>
</table>

*Presence of trisomies ameliorates high risk

Median survival 6-7 years

Median survival <3 years

Leadership Role in Development of IMWG Response Criteria for Myeloma

LEADING ARTICLE

International uniform response criteria for multiple myeloma

BGM Durie¹, J-L Harousseau², JS Miguel³, J Bladé⁴, B Barlogie⁵, K Anderson⁶, M Gertz⁷, M Dimopoulos⁸, J Westin⁹, P Sonneveld¹⁰, H Ludwig¹¹, G Gahrton¹², M Bek san¹³, J Crowley¹⁴, A Belch¹⁵, M Boccadoro¹⁶, I Turesson¹⁷, D Joshua¹⁸, D Vesole¹⁹, R Kyle²⁰, R Alexanian²¹, G Tricot²², M Attal²¹, G Merlini²², R Powles²³, P Richardson²⁴, K Shimizu²⁵, P Tosi²⁶, G Morgan²⁷ and SV Rajkumar²⁷ on behalf of the International Myeloma Working Group²⁹

¹Aptium Oncology, Inc., Cedars-Sinai Outpatient Cancer Center, Los Angeles, CA, USA; ²Institute de Biologie, Nantes, France; ³University of Salamanca, Salamanca, Spain; ⁴Hospital Clinica, Barcelona, Spain; ⁵MIR T UAMS, Little Rock, Arkansas, USA; ⁶DFCI, Boston, MA, USA; ⁷Mayo Clinic, Rochester, MN, USA; ⁸Alexandra Hospital, Athens, Greece; ⁹University of Gothenberg, Gothenberg, Sweden; ¹⁰Rotterdam, The Netherlands; ¹¹Wilhelminenspital Der Stat Wien, Vienna, Austria; ¹²Karolinska Institutet, Stockholm, Sweden; ¹³Ankara University, Turkey; ¹⁴Cancer Research and Biostatistics, Seattle, WA, USA; ¹⁵Cross Cancer Institute, Canada; ¹⁶University of Turin, Turin, Italy; ¹⁷University of Malmo, Malmo, Sweden; ¹⁸Royal Prince Alfred Hospital, Sydney, Australia; ¹⁹St Vincent's Comprehensive Cancer Center, New York, NY, USA; ²⁰MD Anderson, Houston, TX, USA; ²¹Purpan Hospital, Toulouse, France; ²²University of Pavia, Pavia, Italy; ²³The Leukemia and Myeloma Program, Wimbledon, UK; ²⁴Dana Farber Cancer Institute, Boston, MA, USA; ²⁵Nagoya City Midori General Hospital, Nagoya, Japan; ²⁶University of Bologna, Bologna, Italy and ²⁷Royal Marsden Hospital, London, UK
Survival probability

- Poor: 24.7 mos
- Intermediate: 42.3 mos
- Good: 51.0 mos


First Developed Global Genetic Prognostic Model for Myeloma

**All others including**

- $t(11;14)$
- $\Delta 13$
- $t(4;14)$
- $t(14;16)$
- -17p13

$P < 0.001$
Demonstrated that Clinical Activity of a New Myeloma Drug can be predicted by drug response in de novo Vk*MYC mice

Response rate >20% as a single agent in patients
Response rate <20% as a single agent in patients

PPV=45%  NPV=92%

Response is >50% reduction in paraprotein

Updated from Chesi et al. Blood 2012
Pioneered out patient transplant for myeloma with lowest complication rate reported

Autologous Stem Cell Transplant in 716 Patients With Multiple Myeloma: Low Treatment-Related Mortality, Feasibility of Outpatient Transplant, and Effect of a Multidisciplinary Quality Initiative

Morie A. Gertz, MD; Stephen M. Ansell, MD, PhD; David Dingli, MD, PhD; Angela Dispenzieri, MD; Francis K. Buadi, MD; Michelle A. Elliott, MD; Dennis A. Gastineau, MD; Suzanne R. Hayman, MD; William J. Hogan, MBBCh; David J. Inwards, MD; Patrick B. Johnston, MD, PhD; Shaji Kumar, MD; Martha Q. Lacy, MD; Nelson Leung, MD; Ivana N. M. Micallef, MD; Luis F. Porrata, MD; Barbara A. Schafer, RN; Robert C. Wolf, PhD; and Mark R. Litzow, MD

We report on the feasibility of outpatient transplant in 716 pa...
Development of New Drugs in Multiple Myeloma

1999-2010
- Co-investigator in Summit Trial that led to approval of bortezomib
- Led trials that led to approval of thalidomide
- First published phase II of lenalidomide

2011-2015
- Led pivotal trial that led to full approval of carfilzomib
- First published phase II of ixazomib
- First published phase II of pomalidomide

2016-
- Led first phase I/II of isatuximab
- First published phase II of dinaciclib
Led trial that led to approval of thalidomide in myeloma
ECOG/CTSU Randomized Phase III Trial (E1A00)

Best Response within 4 Cycles using ECOG criteria
198 of 202 eligible pts

- Thal/Dex: 63%
- Dex: 41%

1-sided p-value=0.002

Led trial that showed low-dose Dex improves survival

Established the Rd regimen that is now backbone for many myeloma regimens

Led first published phase II of Pomalidomide in Myeloma

Led trial that led to full approval of carfilzomib in myeloma. KRd vs Rd: Aspire Trial

A

![Graph showing progression-free survival comparison between Carfilzomib Group and Control Group.]

- **Disease progression or death — no. (%)**
  - Carfilzomib Group: 207 (52.3)
  - Control Group: 224 (56.6)

- **Median progression-free survival — mo**
  - Carfilzomib Group: 26.3
  - Control Group: 17.6

- **Hazard ratio for carfilzomib group vs. control group (95% CI)**
  - Carfilzomib Group: 0.69 (0.57–0.83)

- **P=0.0001**

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Carfilzomib Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=396)</td>
<td>(N=396)</td>
</tr>
<tr>
<td>Disease progression or death — no. (%)</td>
<td>207 (52.3)</td>
<td>224 (56.6)</td>
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<td></td>
</tr>
</tbody>
</table>

Figure Response with increasing duration of therapy (A) and waterfall plot of best M-protein response (B) among 52 response-evaluable patients treated at the recommended phase 2 dose. One patient in phase 2 was excluded from the response-evaluable population.

### First phase 1 trial of Venetoclax in Myeloma
Demonstration of single agent activity

<table>
<thead>
<tr>
<th>Objective response rate</th>
<th>Evaluable patients with t(11;14) (n=17)</th>
<th>Evaluable patients without t(11;14) (n=26)</th>
<th>All evaluable patients (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>2 (12)</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Very good PR (VGPR)</td>
<td>2 (12)</td>
<td>1 (4)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minimal response</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>5 (29)</td>
<td>12 (46)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Disease progression (PD)</td>
<td>6 (35)</td>
<td>12 (46)</td>
<td>18 (42)</td>
</tr>
</tbody>
</table>

Kumar S. et al. ASH 2015
First described association of myeloma with reversible pulmonary hypertension

Severe reversible pulmonary hypertension in smoldering multiple myeloma: two cases and review of the literature

Wayne L. Feyereisen,¹ Eric R. Fenstad,² Robert B. McCully,² Martha Q. Lacy³

¹Division of General Internal Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; ²Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; ³Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA
Leading Current National Trial for Newly Diagnosed Myeloma

E4A03: Phase III – Newly Diagnosed Myeloma
PI: Shaji Kumar

Randomization

KRd x 12 cycles

VRd x 12 cycles

Revlimid X 2 years

Revlimid Until prog

Continue therapy till prog. or toxicity

Continue therapy till prog. or toxicity

Actively Accruing
Developed Classification of amyloidosis by laser microdissection and mass spectrometry based proteomic analysis in clinical biopsy specimens.
Developed Amyloid Proteome Signature

Figure 1. Identification of a proteome specific for amyloid deposition in SFA specimens. Distribution of the normalized protein spectral counts (the median and percentile distribution) for three amyloid markers (A) APOE, (B) SAP and (C) APOA4 and one control marker (D) APOA1 are shown for Congo red (CR) negative/no amyloid (n=31) and CR-positive/amyloid (n=43) cases of the validation cohort. APOE, SAP and APOA4 are only seen in SFA specimens involved by systemic amyloidosis and, therefore, provide a proteomic signature for amyloidosis. In contrast, APOA1 is present in SFA specimen not involved by amyloidosis suggesting that it is a constituent of normal adipose tissue.

Developed Staging for AL amyloidosis,
Mayo AL Staging, v2.0

**Troponin T**

TnT <0.035 mcg/L  
NT-proBNP <332 ng/L

**Troponin I**

TnI <0.1 mcg/L  
NT-proBNP <332 ng/L

Dispenzieri et al. Journal of Clinical Oncology 2004;122:3751-7
Developed Staging System for AL Amyloidosis, Mayo AL Staging v 3.0 \((n=758)\)

Risk factors: 1 point each for score 0-3 \(\rightarrow\) Stage 1-4

- FLC-diff \(\geq 180\) mg/L
- cTnT \(\geq 0.025\) mcg/L
- NT-ProBNP \(\geq 1,800\) ng/L

Developed definition of MM in patients with AL Amyloidosis

Overall survival in patients with >10% BMPC similar to patients with end-organ damage (CRAB)

First published study of CyBorD in AL Amyloidosis
The current standard frontline treatment

Brief report

Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis

Joseph R. Mikhael¹, Steven R. Schuster¹, Victor H. Jimenez-Zepeda², Nancy Bello¹, Jacy Spong¹, Craig B. Reeder¹, A. Keith Stewart¹, P. Leif Bergsagel¹, and Rafael Fonseca¹
Defined Role of transplantation in AL amyloidosis

ORIGIONAL ARTICLE
Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis

MA Gertz¹, MQ Lacy¹, A Dispenzieri¹,²,³, SK Kumar¹, D Dingli¹,³, N Leung¹,⁴, WJ Hogan¹, FK Buadi¹ and SR Hayman¹

Original Article

Ten-Year Survival After Autologous Stem Cell Transplantation for Immunoglobulin Light Chain Amyloidosis

Stefan Cordes, MD, PhD¹; Angela Dispenzieri, MD¹,²; Martha Q. Lacy, MD¹,²; Suzanne R. Hayman, MD¹,²; Francis K. Buadi, MD¹,²; David Dingli, MD, PhD¹,²; Shaji K. Kumar, MD¹,²; William J. Hogan, MB, BCh¹,²; and Morie A. Gertz, MD¹,²
Developed Transplant Eligibility Criteria for AL Amyloidosis

- Troponin T <0.06 mcg/L
- Troponin T ≥0.06 mcg/L

100 day mortality, 25%
P < 0.0001

- NT-proBNP < 5000 pg/L
- NT-proBNP ≥ 5000 pg/L

10 month mortality, 25%
P = 0.0003

Pioneered Treatment of AL Amyloidosis with Sequential Heart and Stem Cell Transplantation

Pioneered treatment of AL Amyloidosis with Sequential Kidney and Stem Cell Transplantation

Developed Len-Dex in AL Amyloidosis

Figure 2. Response to therapy. (A) Intention-to-treat analysis. (B) Patients receiving at least 3 cycles of treatment and fulfilling the design option to have dexamethasone added to the treatment program.

Developed CRD for AL Amyloidosis

Figure 1. Kaplan-Meier curves showing the median hematologic or organ PFS and OS from enrollment. The median hematologic or organ PFS was 7.4 months (95% CI 5.4-16.1). The median OS for the entire cohort was 37.8 months (95% CI 12.3-NR).

Figure 2. Kaplan-Meier curves comparing the OS of patients with respect to the cardiac biomarker staging. The median OS was not reached for patients in stage I compared with stage II 37.8 months (95% CI 17.5-NR), and 7 months (95% CI 4.2-12.3) for patients in stage III; log rank \( P < .001 \).

Developed Pomalidomide-Dex for AL Amyloidosis

First-in-Human Phase I/II Study of NEOD001 in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction

Morie A. Gertz, Heather Landau, Raymond L. Comenzo, David Seldin,‡ Brendan Weiss, Jeffrey Zonder, Giampaolo Merlini, Stefan Schönland, Jackie Walling, Gene G. Kinney, Martin Koller, Dale B. Schenk, Spencer D. Guthrie, and Michaela Liedtke

ABSTRACT

Purpose

Light chain (AL) amyloidosis is caused by the accumulation of misfolded proteins, which induces the dysfunction of vital organs. NEOD001 is a monoclonal antibody targeting these misfolded proteins. We report interim data from a phase I/II dose-escalation/extension study of NEOD001 in patients with AL amyloidosis and persistent organ dysfunction (NCT01707264).
Developed Response Criteria for AL amyloidosis

Definition of Organ Involvement and Treatment Response in Immunoglobulin Light Chain Amyloidosis (AL): A Consensus Opinion From the 10th International Symposium on Amyloid and Amyloidosis

Morie A. Gertz,1* Ray Comenzo,2 Rodney H. Falk,3 Jean Paul Fermand,4 Bouke P. Hazenberg,5 Philip N. Hawkins,6 Giampaolo Merlino,7 Philippe Moreau,8 Pierre Ronco,9 Vaishali Sanchorawala,3 Orhan Sezer,10 Alan Solomon,11 and Giles Grateau12

1 Dysproteinemia Clinic, Mayo Clinic, Rochester, Minnesota
2 Hematology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York
3 Amyloid Treatment and Research Program, Boston University, School of Medicine, Boston, Massachusetts
4 Hôpital Saint-Louis, Paris, France
5 Department of Rheumatology, University Hospital, Groningen, The Netherlands
6 The National Amyloidosis Center, Department of Medicine, Royal Free Hospital, London, England
7 Amyloid Center, Biotechnology Research Laboratory, University Hospital, IRCCS Policlinico, San Matteo, Pavia, Italy
8 Department of Hematology, University Hospital, Nantes, France
9 Inserm 489 Nephrology Service, Hospital Tenon, Paris, France
10 Myeloma and Lymphoma Research Unit, Hospital Charite, Department of Hematology and Oncology, Humboldt University, Berlin, Germany
11 Human Immunology and Cancer Program, University of Tennessee, Graduate School of Medicine, Knoxville, Tennessee
12 Public Assistance Hospital, Hôtel-Dieu, Paris, France
Led validation of response criteria for AL amyloidosis

Survival of 649 patients based on hematologic response at 6 months

CR (97 patients, 3.6 deaths/100 py)
VGPR (233 patients, 9.6 deaths/100 py)
PR (140 patients, 23.7 deaths/100 py)
NR (179 patients, 47.2 deaths/100 py)
p=0.01
p<0.001

Survival of 377 patients with baseline NT-proBNP ≥650 ng/L according to NT-proBNP response and progression at 6 months

NT-proBNP progression (at least 300 ng/L and 30% increase), 169 patients
NT-proBNP stable, 108 patients
NT-proBNP response (at least 300 ng/L and 30% decrease), 100 patients
p<0.001

Largest US experience with familial amyloidosis

Amyloid: The Journal of Protein Folding Disorders
Volume 22, Issue 2, 2015

Original Article
Hereditary ATTR amyloidosis: a single-institution experience with 266 patients
POEMS SYNDROME
Major Contributions in Patients with POEMS Syndrome

1. Largest single institution series — presentation/outcomes
2. Diagnosis
   - Unique bone marrow findings
   - Platelet count to differentiate from CIDP
   - VEGF to differentiate POEMS from other diseases
3. Treatment
   - Expectations with radiation therapy
   - Expectations with ASCT
   - First report of lenalidomide
   - First report of cyclophosphamide-bortezomib-dex
4. Prognosis
   - High platelets $\rightarrow$ risk for stroke
   - Low albumin $\rightarrow$ risk for relapse
Demonstrated that Overall Survival in POEMS Syndrome Better than Previously Reported

Median 13.8 years

Demonstrated unique BM Findings in POEMS: lymphoid aggregates rimmed by PC & megakaryocyte atypia

- 33 of 67 cases had lymphoid aggregates
- 32 of these had clonal PC
- 59/67 had mega, rimming, or clonal PC

Defined Role of Primary Radiation therapy for POEMS Syndrome (n=38)

- 4 year OS 97%

Risk factors for failure:
- DLCO<70%
- Elevated urine protein

Failure defined as receiving a new treatment
Median follow-up: 43 months

Demonstrated Role of Stem Cell Transplant for POEMS

Between 3/1999-10/2011, 59 patients had ASCT

Median follow-up of 40 months (0-147 months).

Demonstrated Improvement in Peripheral Neuropathy with ASCT in POEMS

Figure 2: Improvement in mRS score following autologous stem cell transplantation.

Median mRS score decreased from 3.0 at t0 to 2.0 at t1 (p < 0.0001) and from 2.0 to 1.5 at t2 (p = 0.25). Box = 25th and 75th percentiles; bars = minimum and maximum values. mRS = modified Rankin Scale.

Waldenstrom Macroglobulinemia (WM)
First genetic and genomic studies in WM
Lack of IgH translocations and 6q deletions in 50%
Described flare of Waldenstrom after Rituximab

Initial Immunoglobulin M ‘Flare’ after Rituximab Therapy in Patients Diagnosed with Waldenstrom Macroglobulinemia

An Eastern Cooperative Oncology Group Study

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BACKGROUND. The goal of the current study was to characterize the initial upsurge in immunoglobulin M (IgM) levels after treatment with rituximab in patients with Waldenstrom macroglobulinemia (WM).

METHODS. As part of a Phase II Eastern Cooperative Oncology Group study, 72 patients were treated with rituximab (375 mg/m² weekly for 4 weeks) between April 2000 and January 2002. IgM levels in these patients were measured at five separate time points so that any temporal changes that occurred could be characterized.

RESULTS. Of the 54 patients for whom the relevant IgM measurements were
Largest US experience with CAD

Review Article

Cold agglutinin disease

Paul L. Swieciicki, Livia T. Hegerova, and Morie A. Gertz

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Cold agglutinin disease is a rare and poorly understood disorder affecting 15% of patients with autoimmune hemolytic anemia. We reviewed the clinical and pathologic features, prognosis, and management in the literature and describe our institutional experience to improve strategies for accurate diagnosis and treatment. Median age at diagnosis was 72 years (range, 43 to 91 years). Median survival of all patients was 10.6 years, and 68 patients (76%) were alive 5 years after the diagnosis. The most common symptom was acrocyanosis (n = 39 [44%]), and many had symptoms triggered by cold (n = 35 [39%]) or other.
Rare Plasma Cell Disorders
Clinical and Genetic Description of Plasma Cell Leukemia

FISH (MGUS n=184, SMM n=116, relapsed MM n=62 and PCL n=26)
aCGH (newly diagnosed MM n=224, relapsed MM n=158 and HMCLs n=48)
p 53 mutational status was evaluated in relapsed MM (n=84) and HMCLs (n=48)

Studied 8 patients with 17p deletions at RR 7 did not have deletion at diagnosis

*Tiedemann et al. Leukemia. 2008; 22, 1044-1052
First published report of stem cell transplant for TEMPI syndrome

Leukemia (2015) 29, 2414-2416; doi:10.1038/leu.2015.298; published online 17 November 2015

Long-term complete clinical and hematological responses of the TEMPI syndrome after autologous stem cell transplantation

S S Kenderian¹, F G Rosado², D B Sykes³, J D Hoyer² and M Q Lacy¹
First to publish stem cell transplantation for scleromyxedema

Successful Treatment of Scleromyxedema With Autologous Peripheral Blood Stem Cell Transplantation

Martha Q. Lacy, MD; William J. Hogan, MRCPI; Morie A. Gertz, MD; Angela Dispensieri, MD; S. Vincent Rajkumar, MD; Suzanne Hayman, MD; Shaji Kumar, MD; Mark R. Litzow, MD; Arnold L. Schroeter, MD