Multiple Myeloma: History

- **1845**: Soft bones, heat soluble protein in urine
- **1873**: Termed Multiple Myeloma
- **1903**: Lytic bone lesions on X-ray
- **1939**: Protein electrophoresis
- **1950**: Immunofixation (IFE)
- **1956**: Bence Jones proteins and IgG
- **1962-69**: Melphalan, MP, Cytoxan
- **1982-86**: VAD, AlloBMT, AutoBMT
- **1996**: Biphosphonates, AutoBMT
- **1999**: Thalidomide
- **2000-02**: GEP
- **2001-2004**: Mini-allo, ISS
- **2003-06**: Bortezomib, Lenalidomide
- **2006**: Doxil
- **2006-09**: Combo’s
- **2009-02**: GF
- **2003-06**: Bortezomib, Lenalidomide

Multiple Myeloma: Epidemiology

- Approx 19,000 new cases in US/yr
  - 1% of all cancers
  - 10% of Heme malignancies
- Prevalence is 45-50,000 patients
  - Median Age 66 years
    - <50 years old: 10%
    - <40 years old: 2%
  - Increased in African Americans
  - Males >> Females

Multiple Myeloma: Pathogenesis

- MGUS is a pre-malignant condition
  - B-Cell Somatic mutation in IgH
    - IgH gene juxtaposed to partner genes
    - Frequent partners: CCND1, FGFR3, MAF
- Subsequent mutations promote growth
  - RAS, PTEN tumor suppressor genes
  - Late events P53, Myc
- Malignant phenotype
  - Stromal cell dependence
  - Cytokine dependence (IL-6)
  - Enhanced angiogenesis

Most Important Questions for the Diagnosis and Treatment of Multiple Myeloma

- What are the Most Important Studies needed at Diagnosis and Follow-up?
- What is the Best Initial Treatment Regimen for Patients with Newly Diagnosed MM?
  - Transplant vs non-transplant candidate?
  - How many cycles do we give?
  - What is the BEST Therapeutic Goal of Treatment ...CR?
- In the new ERA of novel agents what is the Role of Autologous Transplantation?
- Is Maintenance Therapy Needed?
Myeloma Evaluation
- CBC, Lytes, Cr, Ca²⁺, Albumin
- Quantitative immunoglobulins, β2 microglobulin
- SPEP, SIFE, SFLC
- 24 hour urine for UPEP, UIFE
- Skeletal survey, MRI spine
- BM/Bx: H+E, Flow, cytogenetics
- Molecular Studies: FISH, GEP, PCR
- Optional: PET, bone density exam, CRP
- Future: markers for apoptosis

International Staging System (ISS)
- Stage I
  - B2M < 3.5 mg/L
  - Albumin ≥ 3.5
  - 62m
- Stage II
  - B2M < 3.5
  - Albumin < 3.5 g/dL
  - 45m
  - B2M ≥ 3.5 – 5.5
- Stage III
  - B2M > 5.5
  - 29m

Myeloma Evaluation- SLCF
- Serum Free Light Chain
  - Assay detects only free LC
  - Quantitative
  - Should be correlated to
  - 24 hour urine and UPEP
  - Excellent for following response in LC myeloma
  - Not used for CR definition

Myeloma Evaluation
- Molecular Studies:
  - FISH
    - Del 13
    - Del 17p Poor prognosis
    - t(4,14), t(14,20)
    - t(11,14)
  - Gene Expression Profile
    - 70 gene data set (17 genes important)
    - Identifies 15-25% of patients with poor prognosis
    - TT2: high risk GEP 3yr OS 54%

Best Initial Treatment of Myeloma
- Age and Performance Status
- Transplant or Non-transplant Candidate
- High-Risk
  - B2M
  - Genetic and Molecular studies
- What are the treatment goals?
  - CR, VGPR, PR
  - Cure vs. Control

Does Response Matter?
- Depth and TTP
  - PR
  - CR
  - sCR
  - MRD

PCR, MRI, Flow-cytometry
CR and Survival

- Alexanian et al; Bone Marrow Transplant. 2001 May;27(10):1037-43
  - VAD f/b Mel AutoSCT
  - Overall survival: CR PR
    - Survival from CR same from transplant or non-transplant therapy

- Barlogie et al; Cancer. 2008 July; 113(2):355-59
  - TT1: post-transplant survival
  - VAD f/b Mel AutoSCT
  - Overall survival: CR PR
    - Survival from CR same from transplant or non-transplant therapy

- MPE: May; 27(10):1037-43

- Initial Therapy for Myeloma: 2000’s +
  - Rapidly Evolving, Many Options
    - 5 Active treatments
      - Thalidomide
      - Lenalidomide
      - Bortezomib
      - Pegylated Liposomal Doxorubicin (PLD)
      - Autologous Stem Cell Transplant
  - Experimental Therapy
    - New targeted agents
    - Allogeneic Stem Cell Transplantation

- Experimental Therapy
  - 5 Active treatments

- Maintenance
  - Thalidomide 100 mg daily until progression
  - Prednisone 40 mg/m2 PO, d 1–7
  - Melphalan 4 mg/m2 PO day 1-7
  - Cycles 1–6

- MP:
  - Prednisone 40 mg/m2 PO, d 1–7
  - Melphalan 4 mg/m3 PO day 1–7
  - Cycles 1–6

- MP:
  - Prednisone 40 mg/m3 PO, d 1–7
  - Cycles 1–6

- VAD f/b Mel AutoSCT
  - Overall survival: CR PR
    - Survival from CR same from transplant or non-transplant therapy

- Initial Therapy for Non-Transplant Candidates

- Gimmema Randomized Trial
  - Patients aged >55
    - Results: CR vs MP
      - MP vs VMP

- Initial Therapy for Non-Transplant Candidates

- Vista Trial: VMP vs MP
  - Elderly, non-transplant
  - CR higher in VMP (30%) vs MP (4%)
  - CR associated with
    - Longer TTP (HR 0.45)
    - Longer TFI (HR 0.37)
    - Longer OS (HR 0.59)

- Conclusion: Data supports
  - Continuing therapy until CR

- CR and Outcome (ASH Abstract 2778)

- Initial Therapy for Non-Transplant Candidates

- VISTA study design: Newly Dxed MM

- Gimmema study: Newly Dxed MM


- Gimmema Randomized Trial:
  - Patients aged >55
    - Results: CR vs MP
      - MP vs VMP

- Initial Therapy for Non-Transplant Candidates
**VMPT vs VMP in Newly Diagnosed MM: Efficacy**

- **OS:** ~36% reduced risk of death on VMP
- **PFS:** 74% vs 70%
- **TTP:** >4 cycles
- **RR:** 50% vs 42%

**VMP: Poor Prognostic Characteristics**

- **Age <75 years (N=237):** 23.1 months (59 events)
- **Age ≥ 75 years (N=107):** not reached (24 events)
- **CrCI <60 mL/min (N=185):** median not reached (40 events)
- **CrCI ≥ 60 mL/min (N=159):** 21.7 months (43 events)

**E4A03: 1- and 3-yr OS**

- **1-yr OS:** 96% for LD, 87% for Ld
- **3-yr OS:** 78% for LD, 75% for Ld

**VMP Patients Who Received Bortezomib >4 Cycles**

- **OS:** ~36% reduced risk of death on VMP
- **PFS:** 74% vs 70%
- **TTP:** >4 cycles
- **RR:** 50% vs 42%

**Phase III Study of Bortezomib, Melphalan, Prednisone (VMP) ± Thalidomide (VMPT) in Newly Diagnosed MM**

- **VMP:** Poor Prognostic Characteristics
- **VMP Best Response:** VGPR 42% vs 24%
- **VMP: Median OS:** Not reached (111 deaths); 3-year OS rate = 59%

**Initial Therapy for Non-Transplant Candidates**

- **ECOG: E4A03**
  - **LD vs Ld (Age ≥ 65 years)**
  - **Randomized ECOG Trial (~450 patients)**
  - **Len 25 mg D1-21 + Dex 40 mg x 12d or 4d/28 d**
  - **Results**
    - **LD**
      - **RR:** ≥ PR 79%, PR 68%, p=0.008
      - **CR:** 17%, p=0.008
    - **Ld**
      - **OS:** 1/2 yr 84/67%, 95/82%, p=0.001
      - **Early Deaths:** 5%, 0.3%, p=0.003