Multiple myeloma
Biological & Clinical Aspects

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Introduction

Multiple myeloma = Kahler’s disease

Sara Newbury, 1844

“Mollities ossium”
(“soft bones” disease)

Dr. Otto Kahler
1% of all cancers
~10% of all haematological malignancies
incidence 4.5–6.0/100 000/year
median age at diagnosis 72 years
mortality 4.1/100 000/year

Premalignant stages:
1/ MGUS = Monoclonal gammopathy of undetermined significance
Almost all patients with MM evolve from this stage

2/ SMM = smouldering (or indolent) MM
An intermediate but more advanced asymptomatic stage
Biological aspects of Multiple Myeloma
Ontogenesis of myeloma:
A plasma cell disease

→ Proliferation of malignant plasma cells in the bone marrow

→ Production of an abundance of abnormal proteins (paraprotein)
Ontogenesis of myeloma: A mature B cell malignancy

**Germinal center**

- Centrocye
- Centroblast

- Plasmablast
- Memory B cell

**Peripheral blood**

- Activated B cell
- Plasmablast
- Naïve B cell
- Plasma cell

**Multiple Myeloma**

- Immature B lymphocyte
- Pre-B cell
- Pro-B cell
- Stem cell

Bone Marrow

Bianchi & Munchi Blood 2015
Genotypic characteristics of the Plasma cell clone

MM is genetically highly complex
- no single cytogenetic abnormality is typical or diagnostic of MM
- all pts have cytogenetic abnormalities
- genomic instability is a prominent feature of MM cells

• Chromosome translocations (mainly involving IgH locus on chr 14q32)
  This results in upregulation of oncogenes

• Numerical chromosomal abnormalities
  • Non-hyperdiploid (monosomy/del 13; gain 1q, deletion 17p)
    • Associated with high prevalence of IgH translocations : t(4,14) and t(14,16)
  • Hyperdiploid : associated with recurrent trisomies involving odd chromosomes (3,5,7,9,11,15,19)

• Mutations
• Methylation modifications
• Gene and miRNA dysregulation
Multistep pathogenesis & drug resistance

Lymph Node

- GC
- B CELL
- Genetic Mutation(s)
- Somatic Hypermutation
- Isotype Switching

Bone Marrow

- POST GC MUTATED B CELL
- LONG LIVED PC
- MGUS
- SMM
- MM
- S1
- S2

Genetic Events

- Germline Mutations
  - Primary Genetic Mutations
    - IgH Translocations (~43%)
    - Hyperdiploidy (~57%)
- Increased Genomic Instability
  - Translocations, Deletions and Chromosome Gains leading to oncogene overactivity and/or oncosuppressor loss.

Epigenetic Events

- Global Hypomethylation
- Hypermethylation of Target Genes

Biological Events

- CANCER CLONES
  - Proliferation
  - Migration
  - Drug resistance
- MICROENVIRONMENT
  - Pro-tumorigenic soluble factors
  - Pro-tumorigenic ECM
  - Angiogenesis
  - Osteoclastogenesis

- CANCER CLONES
  - Apoptosis
  - DNA Repair
- MICROENVIRONMENT
  - Osteoblastogenesis
  - Immunesurveillance

Bianchi & Munchi Blood 2015
Clonal evolution & Heterogeneity

Clonal evolution in myeloma.

MGUS
SMM
MM
PCL

Clonal advantage

Myeloma Progenitor Cell

<10% >10%

Clinical symptoms

Morgan & Kaiser Hematology 2012
Clonal dynamics in MM

Competition with alternating dominance

Keats et al Blood 2012
Beyond the MM clone: The role of the BM micro-environment

Bianchi & Munchi Blood 2015
The BM niche als therapeutisch target

- Perivascular cell (CXCL12+)
- Osteoblast
- Osteoclast
- Endothelial cell
- Mesenchymal stromal cell
- Plasmacytoid dendritic cell
- NK cell / Cytotoxic Lymphocytes
- Tumor associated macrophage
- Myeloid-derived suppressor cell

Proteosome inhibitors

IMiDs

OSTEOLYSIS

OSTEOLYSIS

ANGIOGENESIS

IMMUNE ESCAPE

PROLIFERATION

Daratumumab

VGEF

DKK1

MIP1a

RANKL

IL-6

IC-1

CXCL12

IL-10

PD1-PD1L

Daratumumab
Clinical aspects of Multiple Myeloma
Symptoms related to:
* the infiltration of PC into the bone or other organs
  • kidney damage from excess light chains.

Spectrum of disease:

Anemia – 73%
- normocytic or macrocytic
- in 97% present at some time during disease course (< 12g/dl)
- related to BM replacement of renal failure

Bone pain – 58%
- particularly in the back of the chest; extremities less often
- usually induced by movement

Renal disease – 48%
- increased serum creat > 2 mg/dl
- caused by light chain nephropathy (“myeloma kidney”) or by hyperCa
- DD amyloidosis
Spectrum of disease:
Fatigue/generalized weakness – 32 %

Hypercalcemia – 28 %

Weight loss – 24 % one-half of whom had lost ≥9 kg

Neurological disease
rare at presentation but spinal cord compression is a medical emergency!

Increased risk for infections
< combined immune dysfunction and physical factors (ex hypoventilation)
most frequently caused by pathogens incl Str. Pneumoniae and Gram /-/ organisms
Besides that:

The diagnosis of MM is co-incidental, in the absence of symptoms, in 25% of the patients.
MM : Further examination
Blood / Urine analysis

• Monoclonal protein – present in 97%
  • Detected by protein electropheresis

• Serum free light chain Kappa / lambda detection (Freelite)
Serum immunofixation:
- confirmation of monoclonality
- Determination of the isotype

IgG – 52%
IgA – 21%
K or L light chain only – 15%

IgD – 2%
Biclonal – 2%
IgM – 0,5%
Negative – 6,5%
MM : Further examination
Special conditions

• **Light chain MM** – 20%
  • Only light chain in serum or urine without expression of Ig heavy chain
  • Higher incidence of renal failure

• **Non – secretory MM** – 3%
  • No M-protein in the serum or urine on immunofixation at the time of diagnosis
  • Detection of monoclonal free light chain – 60%

• **Oligo-secretory MM** - 5-10%
  • Defined as the absence of measurable disease in serum (M protein < 1 g/dl) or urine (M protein < 200 mg/24h)
MM: Further examination
Bone marrow (aspirate & biopsy)

- Key component to diagnosis

- **Morphology**: % plasmacytosis (diagnostic criterium)
  - due to patchy BM involvement, aspirate and biopsy may show < 10% plasma cells

- **Immunophenotype**
  - Detection of kappa or lambda in cytoplasm (surface Ig is absent)
    - NI K/L ratio = 2:1
    - Abnl = 4:1 or 1:2
  - Distinguishes from reactive plasmacytosis
  - Multiparametric flow cytometry that can detect six or more antigens (commonly CD38, CD45, CD56, CD19, kappa, and lambda)

- **Cytogenetics**: FISH analysis
  - no single cytogenetic abnormality is typical or diagnostic of MM
  - Important for risk stratification
MM : Further examination
Evaluation of bone lesions

• Whole – body low dose CT (WBLD-CT)
  • New standard for the diagnosis of lytic disease

• Conventional radiography if CT is not available

• MRI
  • Provides greater details
  • Is recommended when spinal cord compression is suspected
  • Whole body MRI or MRI of the spine and pelvis
  • Assessment of PC infiltration, in particular the presence of bone focal lesions

• PET-CT
  • Evaluation of bone lesions
  • Evaluation of extramedullary plasmacytoma
Diagnosis of MM
Revised IMWG diagnostic criteria

Clonal BM PC ≥10% or biopsy-proven bone or extramedullary plasmacytoma + any one or more of the following myeloma defining events (MDE)

1/ Evidence of **end organ damage** that can be attributed to the underlying PC proliferative disorder (previously called « CRAB »):

- **HyperCa**: serum calcium >1 mg/dL than upper nl limit or >11 mg/dL
- **Renal insufficiency**: Crea clearance <40 mL/min or serum creat >2 mg/dL
- **Anemia**: Hb >20 g/L below lower nl limit or a Hb <10 g/dl
- **Bone lesions**: 1 or more osteolytic lesions on skeletal radiography, CT, or PET-CT

2/ Any one or more of the following **biomarkers of malignancy**:

- Clonal BM PC ≥60%
- Involved:uninvolved serum free light chain ratio ≥100
- >1 focal lesions on MRI studies
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Diagnosis of MM
Revised IMWG diagnostic criteria

• Diagnosis of Multiple Myeloma refers to Myeloma requiring therapy
• Previously: only active (symptomatic) MM was treated
• Currently: the presence of certain biomarkers of malignancy defines a type of MM that must be treated (in the absence of organ damage)
• Definition of “biomarkers of malignancy» :
  • Association with a risk of progression of 80% to symptomatic end-organ damage
Diagnosis of smouldering MM
Revised IMWG diagnostic criteria

**Definition of SMM:**
Both criteria must be met:
1/ Serum M protein (IgG or IgA) $\geq 30$ g/L or urinary M protein $\geq 500$ mg/24h and/or clonal BM PC 10–60%
2/ Absence of myeloma defining events or amyloidosis

**Molecular classification of SMM:**
Subclassification based on underlying cytogenetic abnormalities (FISH)
1/ High risk SMM (median TTP 24m) : t(4,14), 1q gain, del17p
2/ Intermediate risk SMM (median TTP 34m) : trisomies
3/ Standard risk SMM (median TTP 54m) : other incl t(11,14)
4/ Low risk SMM (median TTP 101m) : no cytogenetic abnl

Consequences for therapy for high risk MM
The natural history of MM

- Clonal expansion
- MGUS
- Early myeloma
- Late myeloma
- Plasma cell leukemia

M-protein (g/L)

Asymptomatic

Symptomatic

ACTIVE MYELOMA

MGUS or smoldering myeloma

Plateau remission

1. RELAPSE

2. RELAPSE

REFRACTORY RELAPSE

First-line therapy

Second-line

Third-line