MONOCLONAL GAMMOPATHIES
Monoclonal gammopathies

- MONOCLONAL GAMMOPATHIES (MG)
  - MG – plasma cell or lymphoplasmocytic dyscrasies characterized by the production of the identical whole immunoglobulin chain or chain fragment, which is evidence for monoclonality
    - the monoclonal protein product of plasma cell, lymphocyte cell population is called as M-protein, monoclonal immunoglobulin (MIG) and paraprotein respectively
    - clinical situations characterized by the occurrence of an M-protein may be malignant or nonmalignant
  - Laboratory evaluation of M-proteins and/or plasma cell dyscrasias
    - serum/urine protein electrophoresis
      - a common screening test for an M-protein depends on the rate of migration of proteins in an electric field
      - molecules of each M-protein have identical size and charge and thus migrate as a narrow band
    - immunoelectrophoresis and immunofixation electrophoresis
      - used to identify the exact heavy chain class and light chain type in M-proteins
    - serum viscosity – IgM and/or IgA paraproteins form multimers and elevate the serum viscosity
      - the relative viscosity of normal serum in relation to destilled water is 1.8
    - serum free lights chains – Freelite test, measurement of serum concentrations of kappa and lambda chains and its ratio (kappa/lambda ratio)
    - cryoglobulins – proteins that precipitate in the cold (< 37°C) and redissolve when heated
Classification of monoclonal gammopathies (R.A.Kyle, 1996)

- MG –characterized clonal plasma cell proliferation with production of monoclonal immunoglobulin (MIG, „paraprotein“) or chain fragments

I. MONOCLONAL GAMMOPATHY of UNDETERMINED SIGNIFICANCE (MGUS)
   A. Benign (IgG, IgA, IgM, FLC kappa or lambda)
   B. Neoplastic diseases and conditions without usual presence of MIG
   C. „Idiopathic“ Bence-Jones proteinuria κ or λ (MGUS κ or λ)

II. MALIGNANT MG
   A. Symptomatic/Multiple myeloma (IgG, IgA, B-J, IgD)
      1. Active MM
      2. Smoldering MM (SMM)
      3. PCL
      4. Nonsecretory MM
      5. Osteosclerotic myeloma (POEMS syndrome)
   B. Plasmocytoma
      1. Solitary bone plasmocytoma
      2. Extramedullary plasmocytoma
   C. Malignant lymphoproliferative conditions
      1. Primary (Waldenström) macroglobulinemia (MW)
      2. Malignant lymphomas (NHL, CLL)
   D. Heavy chain disease (α, γ, μ)

III. CRYOGLOBULINEMIA

IV. PRIMARY SYSTEMIC – AL AMYLOIDOSIS
Monoclonal gammopathies *(Mayo clinic 1960-1995, n=21079)*

- **MGUS (62%)**
- **MM (18%)**
- **Solitary extramedullary plasmocytoma (2.5%)**
- **SMM (3%)**
- **Lympho proliferative disorders (1.8%)**
- **AL (8%)**
- **MW (2%)**
- **Other (2%)**
Plasma Cell Neoplasms

- MGUS
- Smoldering MM
- Active MM
- Extramedullary MM
- Cell line

Clonal cells

> 10%

End organ damage

BM independence
MULTIPLE MYELOMA

MM – clonal, uncontrolled proliferation and accumulation of neoplastic transformed elements of B-cell line i.a. plasmocytes (CD\textsubscript{138}+) with production of MIG („paraprotein“) detected in serum and/or urine and with myeloma related organ dysfunction „CRAB“
MM – etiopathogenesis of multiple myeloma I

- MM – is a malignant disease caused by neoplastic monoclonal proliferation of bone marrow plasma cells, characterized:
  - plasma cell accumulation in the BM
  - presence of MIG in the serum and/or urine
  - specific organ dysfunction (CRAB) (hyper-Calcaemia, Renal damage, Anaemia and by Osteolytic lesions, i.a. Myeloma Bone disease)

- MM – etiology and pathogenesis (1)
  - environmental radiation and chemical exposure are associated with an increased incidence of MM
  - cytogenetic and oncogene abnormalities occur in a high percentage of patients with myeloma
    - DNA aneuploidy, IgH gene rearrangements, expression of the BCL-2 protein etc.
MM – etiopathogenesis of multiple myeloma II

- **MM – etiology and pathogenesis (2)**
  - **chromosome abnormalities** were found in ~ 90% or patients with FISH and microarray techniques
    - deletion of chromosome 13 and hypodiploidy have been shown to be associated with poor survival as have t(4;14), t(14;16)
    - c-Myc RNA and protein overexpression, N- and K-RAS mutations (~ 50%)
    - mutations and deletions in the retinoblastoma and the p53 tumor suppressor genes in malignant plasma cells
    - multidrug resistance (MDR) gene
  - **cytokines are involved**
    - IL-6 is an autocrine growth factor
    - IL-1 and TNF-\(\alpha\)
  - **elevation of proliferation rate** and low apoptosis rate of myeloma cells → \(\uparrow\) accumulation of myeloma cells
  - **contact with marrow stromal cells** appears to be required for the complete expression of the malignant repertoire of myeloma cells
MM – pathophysiology

- MM – uncontrolled growth of myeloma cells has many consequences (myeloma bone disease, MBD)
  - skeleton destruction and hypercalcaemia
  - BM failure
  - increased plasma volume and viscosity
  - suppression of normal Ig production
  - renal insufficiency

- MBD
  - dysregulation of bone remodelling → the typical osteolytic lesions and/or osteoporosis
  - osteolytic lesions – increased osteoclastic activity with no increased osteoblast formation of bone
  - ↑ production of RANKL, IL-6, IL-1β, MIP, etc. by myeloma and stromal cells → ↑ stimulation of OCL formation and activity
  - osteoprotegerin inhibits OCL activity → RANKL/OPG ratio in pathogenesis of MBD
  - the most commonly affected areas are in the spine, skull, pelvis and ribs
BMPC

- **Bone marrow infiltration** with plasma cells resulting in – anaemia, neutropenia, thrombocytopenia

- **Overproduction of MIG** – hyperviscosity syndrome
  - MIG – IgG (~ 50-60%), IgA (~ 20%), Bence-Jones (κ or λ) (~ 15%), IgD, IgM, biclonal and nonsecretory type à ~ 1-2%

- **Reduction in the normal Ig levels** („immune paresis“)
  - Tendency to recurrent infections *(particularly of respiratory tract)*

- **Renal impairment** – combination of
  - Deposition of light chains in the renal tubules *(cast formation)*
  - Hypercalcaemia, hyperuricaemia, use of NSAID
  - Rarely deposition of amyloid
### MM – DIAGNOSTIC CRITERIA
(International Myeloma Working Group, 2003)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All three diagnostic criteria required</td>
<td></td>
</tr>
<tr>
<td>1. Monoclonal BMPC ≥ 10%, and/or presence of biopsy – proven plasmocytoma</td>
<td></td>
</tr>
<tr>
<td>2. MIG present in the serum and/or urine</td>
<td></td>
</tr>
<tr>
<td>3. Myeloma – related organ dysfunction (≥1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Calcium elevation &gt; 2.8 mmol/l</td>
</tr>
<tr>
<td></td>
<td>• Renal insufficiency (S-creatinine &gt; 177 µmol/l)</td>
</tr>
<tr>
<td></td>
<td>• Anaemia Hb &lt; 100 g/l</td>
</tr>
<tr>
<td></td>
<td>• Bone Osteolytic lesions or osteoporosis</td>
</tr>
<tr>
<td></td>
<td>- solitary plasmocytoma</td>
</tr>
<tr>
<td></td>
<td>- osteoporosis Pb ≥ 30%</td>
</tr>
<tr>
<td>• This criteria identify stage I-B and II-III – A/B myeloma by Durie-Salmon stage</td>
<td></td>
</tr>
<tr>
<td>• Stage I-A becomes „smoldering“ or indolent MM</td>
<td></td>
</tr>
</tbody>
</table>
MM – myeloma bone disease, X-ray examination
MM – clinical manifestation

- **MM – incidence**
  - 3-4/100 000/year, variability from country to country (1 in China, 4/100 000 in West Europe)
  - is more common in blacks than white
  - **M/F ratio** is 2-3:2
  - **age median** 61 (63 years), the incidence rises with age

- **MM – clinical manifestation**
  - nonetheless, the disease can remain „asymptomatic“ for many years
  - **disease phases**
    - **asymptomatic** (indolent, „smoldering“ MM, stage I-A according D-S)
    - **symptomatic/“active“** MM
      - remission, eventually „plateau“/stable phase
      - relaps eventually progression
    - **refractory/terminal phase**
MM – the relation of the myeloma pathogenesis and clinical manifestation

IMMUNOSUPPRESSION → INFECTIONS → PANCYTOPENIA

BM - INFILTRATION

MYELOMA CELL
(proliferation / accumulation)

MIG - PRODUCTION

HAEMOSTASIS DAMAGE

ANAEMIA

NEUROPATHIES

HYPERVERVISCOSITY SYNDROME

AL - AMYLOIDOSIS

OSTEOPOROSIS
OSTEOLYSIS
PATHOL.FRACTURES

HYPERCALCAEMIA

RENAL IMPAIRMENT
CLINICAL SYMPTOMS

- Bone pain – most commonly lower back (60%)
  - vertebral involvement (compression/pathological fractures of vertebral bodies)
  - osteolytic bone lesions
  - tumour growth on nerve roots or spinal cord compression

- Features of anaemia
  - lethargy, weakness, dyspnoe, pallor, etc.

- Recurrent infections
  - related to deficient normal immunoglobulins/antibody production and/or cell-mediated immunity
  - bacterial, viral, etc. (frequently pneumonia)

- Symptoms of renal failure (20-30%)
  - nephrotic syndrome – in associated with AL amyloidosis and with B-J-proteinuria

- Hypercalcaemia (20-30%)
  - polydipsia, polyuria, anorexia, vomiting, constipation, mental disturbance
**CLINICAL SYMPTOMS**

- **Abnormal bleeding tendency** (~ 5% IgG – 30% IgA)
  - interference of MIG with platelet function and coagulation factors („acquired coagulopathy“)
  - thrombocytopenia in advanced disease
  - thrombosis in small capillaries – hypercoagulable state (protein deficiency)

- **Hyperviscosity syndrome** (< 10%)
  - more likely with IgA than IgG myeloma (IgG3)
  - symptoms if viscosity is > 4 times that of water
  - headache, malaise and vague, mental status changes (confusion or dementia)
    - purpura, haemorrhages (nose and GIT bleeding)
    - visual disturbance („fundus paraproteinaemicus“) – link sausage appearance of retinal veins and retinal hemorrhages and papiledema
    - congestive heart failure (polymerization of MIG)

- **Polyneuropathy** – perineuronal or perivascular

- **Extramedullary disease**
  - PCL – often with leukaemia meningosis
  - visceral organ (lymph node, liver, spleen, kidneys) infiltration

- **Occasionally** (amyloid disease, 15-20%)
  - macroglossia, carpal tunnel syndrome, diarrhoe, neuropathies, etc.
### MM – Assessment of tumor mass
(staging system Durie-Salmon, 1975)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>Stage - I</th>
<th>Stage - II</th>
<th>Stage - III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb (g/l)</strong></td>
<td>&gt; 100</td>
<td>No stage I and III</td>
<td>&lt; 85</td>
</tr>
<tr>
<td><strong>S-Ca (mmol/l)</strong></td>
<td>≤ 2.9</td>
<td></td>
<td>&gt; 2.9</td>
</tr>
<tr>
<td>Osteolytic lesions</td>
<td>≤ 1 lesion</td>
<td></td>
<td>&gt;3 lesions (fractures)</td>
</tr>
<tr>
<td><strong>S-MIG (g/l)</strong></td>
<td>IgG &lt; 50</td>
<td>0.6-1.2 (intermed.)</td>
<td>&gt;1.2 (high)</td>
</tr>
<tr>
<td><strong>U-BJ (g/24 h.)</strong></td>
<td>IgA &lt; 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of neoplastic plasma cells (x 10^{12}/m^2)</strong></td>
<td>&lt;0.6 (low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Substage</strong></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td><strong>S-creatinine (µmol/l)</strong></td>
<td>&lt; 177</td>
<td>≥ 177</td>
<td></td>
</tr>
</tbody>
</table>

**Cumulative proportion of survivors**

- **Stage 1** (M-77, n-42)
- **Stage 2** (M-41, n-111)
- **Stage 3** (M-15, n-117)

**DURIE - SALMON**
(n-270 – Olomouc, 2005)

- Stage A (M-44, n-203)
- Stage B (M-11, n-67)

**p < 0.001 (log-rank test)**

(months)
MM-S-β₂ microglobulin, survival curves (Kaplan-Meier)

S-BETA₂ MICROGLOBULIN

(Olomouc, 1996)
# MM – ISI staging systems *(IMWG, 2003)*

<table>
<thead>
<tr>
<th>Stage</th>
<th>IPI/ISI</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$B_2M$ (mg/dl)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albumin (g/l)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>$B_2M$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$B_2M$</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>$B_2M$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td></td>
</tr>
</tbody>
</table>

![Cumulative proportion of survivors](image)

*Olomouc, 2005*
Natural History of MM:

- Asymptomatic
- Symptomatic
- Active Myeloma
- Relapse
- Refractory Relapse

M Protein (g/l)

- MGUS* or Smoldering Myeloma
- Plateau Remission

- Therapy

- ~20,000 New cases in U.S.²
- ~60,000 Prevalence in the U.S.
- ~11,000 Annual deaths in U.S.²

*Monoclonal gammopathy of uncertain significance
**MG - DIFFERENTIAL DIAGNOSIS (IMWG, 2003)**

<table>
<thead>
<tr>
<th>MM</th>
<th>SMM (I-A)</th>
<th>Solitary bone plasmocytoma</th>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BMPC</td>
<td>&gt; 10% ev. pos.</td>
<td>10 – 30 %</td>
<td>&lt; 10 % Plasmocytoma (histol.)</td>
</tr>
<tr>
<td>- plasmocytoma/histol.</td>
<td></td>
<td></td>
<td>&lt; 10 % neg.</td>
</tr>
<tr>
<td>2. MIG</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Neg., or</td>
</tr>
<tr>
<td>- serum and/or urine</td>
<td></td>
<td></td>
<td>IgG &lt; 35.0 g/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgA &lt; 20.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>U-B-J &lt; 1.0 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(↓ after radioterapy)</td>
</tr>
<tr>
<td>- Ca &gt; 2.8 (mmol/l)</td>
<td></td>
<td>Neg.</td>
<td>N</td>
</tr>
<tr>
<td>- Creatinine &gt; 177 μmol/l</td>
<td></td>
<td>Neg.</td>
<td>N</td>
</tr>
<tr>
<td>- Hb &lt; 100 g/l</td>
<td></td>
<td>Neg.</td>
<td>N</td>
</tr>
<tr>
<td>- osteolytic lesions and/or osteoporosis and compressive fracture</td>
<td></td>
<td>Neg.(X-ray) ev.1 lesion (X-ray, MR/CT, PET)</td>
<td>N</td>
</tr>
<tr>
<td>- S-albumin</td>
<td>N-↓</td>
<td>N-↓</td>
<td>N</td>
</tr>
<tr>
<td>- Normal S-Ig depression</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>- PC-PI (%)</td>
<td>↑-N</td>
<td>↓-N (&lt; 1%)</td>
<td>↓-N</td>
</tr>
<tr>
<td>- PROGRESSION</td>
<td>Posit.</td>
<td>Stability → progression</td>
<td>Stability → progression?</td>
</tr>
</tbody>
</table>
MM – investigations

- **MIG** – in the serum, urine or both (98%)
  - Bence-Jones in urine in two/thirds of cases
  - diminished levels of an involved Ig classes is common
  - ↑ total protein in the serum
  - FLC serum levels *(Freelite test)*

- **BM** - shows increased plasma cells (> 10%, usually 30-50% in BM aspirate or trephing)
  - „myeloma cells“ – atypical PC, monoclonal cell expressing the same Ig as the S-MIG
  - flow cytometric analysis
    - DNA aneuploidy in 80% patients
    - myeloma cells express positivity of CD138⁺, CD56⁺, CD38⁺, CD45⁻
  - a high proliferative index (PC-propidium iodide) and low apoptotic index (e.g. annexin V) are an important negative prognostic features
  - chromosomal abnormalities – FISH

- **Hematologic abnormalities**
  - normochromic/normocytic anaemia due to marrow replacement by plasmocytes, „rouleaux“ formation
  - trombocytopenia and neutropenia – in the advanced phases of MM
  - coagulopathy – interference with fibrin formation by M-protein
  - abnormal plasma cells in the blood film (15%)
Skeletal survey (x-ray, MRI, CT, FDG-PET/CT) of the axial skeleton
- osteolytic areas without evidence of surrounding osteoblastic reaction or sclerosis (60%)
- generalized bone rarefaction (20%)
- pathological fractures are common
- no bone lesions are found in 20% patients
- MIBI – is valuable detection and follow-up of treatment
- DEXA – evaluation of a grade of skeletal mineralisation

Other laboratory findings
- high ESR (this is almost always very high, > 100 mm/hour)
- serum elevations of: Ca, urea and creatinine (20%), uric acid, ALP (in fractures)
- ↑ $\beta_2$-microglobulin, ↓ S-albumin, ↑ CRP, ↑ LDH, ↑ thymidinekinase → negative PF
- ↑ IL-6, ↑ VEGF, ↑ HGF, etc.
MG – S-FLC (free light chains, Freelite™)

MGUS
n-54

MM
n-116

Bence-Jones

Ostatní MG

V. Ščudla, P. Scheiderka, F. Kouřil, J Minařík et al., 2004
MM – histobiopsy of the bone marrow

Myeloma cell type infiltration

<table>
<thead>
<tr>
<th>Presence (%)</th>
<th>Interstitial</th>
<th>Interstitial sheets</th>
<th>Interstitial nodular</th>
<th>Nodular</th>
<th>Packed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence (%)</td>
<td>58</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Osteol. (%)</td>
<td>12</td>
<td>22</td>
<td>74</td>
<td>79</td>
<td>52</td>
</tr>
<tr>
<td>OS (months)</td>
<td>46</td>
<td>31</td>
<td>22</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

Histological state at the time of biopsy

- Presence (%)
- Osteol. (%)
- OS (months)

Bartl, R. 1996
MM – comparison X-Ray vs. MRI examination of spine

MR vs. X-Ray – examination of the spine

- Positivity: 91% MR, 55% X-Ray
- Vert. body compression: 56% MR, 49% X-Ray
- Spinal caval stenosis: 30% MR, 0% X-Ray
- Extramedular disease: 20% MR, 0% X-Ray
- Osteolytic lesions: 83% MR, 4% X-Ray

J. Nekula, V. Ščudla et al., 1997

M. Vytrássová, V. Vavrdová et al., 2000
**MM – prognostic factors (7)**

- **MM prognosis is determined by both**
  - the number of myeloma cells ("myeloma mass"), Durie-Salmon (D-S) staging system (I-III A/B)
  - the specific properties of myeloma cells
    - growth rate, MIG secretion rate, production of various cytokines, etc.

- **PROGNOSTIC FACTORS**
  - identifications of patients with particularly "poor" versus "very good" prognosis
  - individually type of therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Significance</th>
<th>Factor</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&gt; 65)</td>
<td>Younger-better</td>
<td>Specialized tests</td>
<td>High – poor</td>
</tr>
<tr>
<td>Performance status (0-4)</td>
<td>Low levels-poor</td>
<td>PC - proliferative index</td>
<td>Plasmoblastic – poor</td>
</tr>
<tr>
<td>Routine laboratory</td>
<td>Higher (&gt; 4-6 ng/l)</td>
<td>PC – morphology</td>
<td>Hypodiploidy/deletion 13-poor</td>
</tr>
<tr>
<td>testing</td>
<td>Lower – poor</td>
<td>BM – cytogenetics</td>
<td>13 deletion – poor</td>
</tr>
<tr>
<td>S-β₂-microglobulin</td>
<td>Elevated – poor</td>
<td>Standard cytogenetics</td>
<td>1p/1q, 11q – 17p, del 22q-</td>
</tr>
<tr>
<td>S-albumin</td>
<td>Elevated – poor</td>
<td>FISH analysis</td>
<td>t(4;14), t(14;16), t(1;19)</td>
</tr>
<tr>
<td>S-creatinine</td>
<td>Elevated – poor</td>
<td>Microarray techniques</td>
<td>Extramedullary – poor</td>
</tr>
<tr>
<td>CRP</td>
<td>Lower – poor</td>
<td>Whole-body FDG/PET-CT scan</td>
<td>prognosis</td>
</tr>
<tr>
<td>Hb</td>
<td>Low – poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>Low – poor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OS – influence of cytogenetic changes 0-3

logrank p<0.001

GEP signatures

Shaughnessy et al, Blood 2007, 109(6), 2276-2284
Exclusion of patient with MGUS and smoldering/indolent myeloma

There is yet no optimal consensus as to the best way to manage MM

- MM is not curable!
- patient with asymptomatic/indolent e.g. „smoldering-stable“ MM
  - should be observed closely → „wait/watch and see“ and/or supportive therapy only

Treatment is recommended in active/symptomatic forms of MM

- advanced clinical stage (I-B-II/III-A/B according Durie Salmon)
- when the M-component/other laboratory features are increasing
- clinical problems or complications have emerged or are imminent
- problems sufficient to require treatment include
  - bone lesions (X-Ray, MRI, CT, FDG-PET/CT)
  - renal insufficiency
  - reduced blood count (e.g. anaemia, neutropenia, thrombocytopenia)
  - elevated S-calcium
  - other significant organ or tissue damage caused by MM
Treatment sequence

NEW

Thal/Dex
VD
Rev/Dex
CyBorD
VTD
VRD

SCT
VD/VRD

Nothing
Thalidomide?
Bortezomib?
Lenalidomide

Bortezomib
Lenalidomide
Thalidomide
Carfilzomib
Pomalidomide

Front line treatment

Induction
Consolidation

Maintenance
Post consolidation

Relapsed

Rescue

OLD

VAD
DEX

SCT

Nothing
Prednisone
Thalidomide

Few options
MM – overall summary of treatment options

- BASIC THERAPY
  - Chemotherapy – standard/conventional treatment
  - High dose therapy with autologous transplantation
  - New „biologic“ therapy – „combination with conventional substances“
  - Radiation

- SUPPORTIVE CARE ASPECT
  - emergency care, e.g. hemodialysis, plasmapheresis, surgery, etc.
  - pain medication
  - rHuEPO (e.g. Eprex or Recormon, Darbepoietin)
  - bisphosphonates (e.g. Aredia, Bonefos, Lodronat, Zometa, etc.)
  - antibiotics
  - growth factors (e.g. Neupogen)
  - brace/corset
  - diet

- PERSPECTIVE TREATMENT OPTIONS (?)
  - new vaccines (e.g. antiidiotype)
  - new chemotherapy and biological components
INDUCTION CHEMOTHERAPY

MP – melphalan/prednison

- remains a valid option only for elderly patients (> 80-85 years), pure PS and high commorbidity (now it is not „gold standard“, but historical treatment)
- indication: „low risk“ > 80-85 years
- 40-60% of patients have an „OR“ (objective response), good tolerance, OS – 19-40 months
- melphalan is not recommended if stem cell harvesting is planned
- cyclophosphamide – although less popular, is a valid option (C or CP)
  - similar anti-myeloma activity
MM – conventional chemotherapy

INDUCTION CHEMOTHERAPY

- More complex combination schedules
  - higher and earlier response rate than MP but marginal overall better outcome? (survival time)
  - more toxic inconvenience and expense: VBMCP, VAD ("historical treatment")
- Pulse dexamethasone alone – is widely used as frontline therapy
  (40 mg 1.-4. day) → in renal insufficiency, pancytopenia (response without injuring the BM stem cells!)
- The current trend in "untrasplanted patients" is to use chemo-immunotherapy, eg.: MPT, MPV, R-Dex, ev. BAD, RAD as a first choice
  - more complex ("combination") therapy is also reserved as a back up approach for patients who fail to have a satisfactory response or with severe complications (e.g. spinal cor compression, etc.)
- The major factor which determines outcome is the intrinsic drug sensitivity or resistance of the myeloma cells
THE MOST PROMISING NOVEL BIOLOGIC THERAPIES

THALIDOMIDE

- Thal/Dex – it was active
  - as a frontline approach 50-100 mg/day, minimal myelosupression
  - Thal/Dex, event. MPT or CTD
    - Thal/Dex - ~ 50% OR (↓ to < 50% MIG)
- adverse reaction (~ 25-50%): severe neuropathy, constipation, lethargy, sleepines, skin reaction, etc.

LEDALIDOMID (REVLIMID - thalidomide analogs)

- Revlimid/Dex
  - very good efect, no neurologic side efect, but neutropenia
  - R-Dex, RAD, RVD, RCD, etc.

BORTEZOMIB (VELCADE)

- very good efect in patients with induction therapy and relapsed/refractory myeloma
  - OR ~ 35%, median response ~ 12 months, OS ~ 16 months
- combination Velcade plus Thal, Doxil, Dex, etc.

New compunds: carfilzomib, pomalidomide, panobinostat, etc.

Assessment of all three new drug in the frontline therapy

- very good resultes before ASCT
- primary induction, consolidation with HDT/ASCT, post induction/consolidation and maintenance therapy
Bortezomib Targets MM Cells in the BM Microenvironment

A. Bortezomib

B. Bortezomib

C. Bortezomib

D. Bortezomib

MM Cell Growth

TNFα

VEGF

IL-6

Bone Marrow Stromal Cells

Bone Marrow Vessels

Treatment Choices

Thal
Bortezomib
Carfilzomib

IMiDs + Proteasome inhibitors + Chemotherapy

Pom
Len
Dex
Methylpred
Prednisone

Steroids + Clarithromycin

Anthracyclines
- Doxorubicin
- PLD

Alkylating agents
- Melphalan
- Cyclophosphamide
- Bendamustine

Novel Combinations
Clinical Trials
Investigational Drugs
MM – results of the combined 1. line therapy

Stewart AK, Richardson PG, San Miguel JF Blood (2009)
MM – COMPARISION MP-T vs MP

EVENT FREE PROGRESSION

OVERALL SURVIVAL

MPT

Thal <400mg/day

Palumbo, Lancet 2006; 367: 825-831
MM-015: results in first therapy

**PFS**
- MPR-R: 31 months
- MPR: 15 months
- MP: 12 months

**4-years OS**
- MPR-R: 69%
- MPR: 61%
- MP: 58%

*p* = 0.006

*p* = 0.639

*Palumbo, NEJM, 2012*
MM – high dose therapy with autotransplantation

- HD – THERAPY with AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)
  - HD-Th+ASCT → is the frontline „therapy of choice“ for newly diagnosed patients with symptomatic MM in this time and < 65 years
  - complete remission (CR) rate range from 30-75%, PR from 75-90%
  - This approach is not curative → 90% of patients relapse
    - median overall survival with HDT/ASCT is in 5-6 year range
    - procedure related mortality with HDT/ASCT is very low ~ 1%
  - HD-Th – a more dramatic myeloma cell kill in comparison of conventional therapy – „eradication of myeloma cells“?
MM – high dose therapy with autotransplantation

HD-therapy with ASCT

- **induction therapy**, e.g. CTD (*Thalidomid*), CTV (*Velcade*), R-Dex (*Revlimid*), (↓ „myeloma mass“), R-Dex (*Revlimide*)
- „mobilisation“ and „collection“ of peripheral blood stem cells (PBSC)
  - cyclophosphamide (2-5 g) + G-CSF stimulation (Neupogen)
- „conditioning“ regimen – standard regimen is melphalan 200 mg/m² i.v./1.day
- „transplantation“ of autologous PBSC (intravenously infusion)
  - engraftment of haematopoietic stem cells (~ 2 weeks)
  - supportive therapy (G-CSF, rHuEPO/antibiotics, etc.)
- **maintenance** therapy (<VGPR – Thalidomide, Bortezomib/Velcade or Lenalidomide/Revlimid)

Double or tandem transplantation

- limited contribution
- useful and viable option is relapse after 1. ASCT
MM – HD-therapy/ASCT indications

- **Active/symptomatic/overt form of MM**
  - Age - < 65 (70?) years
  - Performance status (ECOG/WHO) ≤ 2
  - Renal function
    - normal function
    - creatinine clearance 50 ml/min and/or S-creatinine < 3-4.0 mg/dl can be considered for autotransplantation
      - but only at a center with special expertise in this setting
  - Patient without previous therapy: Melphalan, BCNU, extensive X-ray irradiation
  - Absence of advanced phases of „internal diseases“ (↓ low commorbidity)
  - ASCT is possible in ~ 50% of MM patients

- **Role of allogeneic transplantation**
  - despite medical improvements, allogeneic transplant is a high-risk procedure in the management of MM
  - initial treatment – related mortality is high (at least 20-30%)
  - the GV-myeloma effect can be enhanced by using donor lymphocyte infusions (DLI)
  - recent interest is in „non-myeloablative/or mini-allogeneic transplants“ in MM
    - lesser toxicity (but still substantial acute (45%) and chronic (55%) GVH disease
  - indication in younger patients particularly with on HLA-matched, sibling donor of the same gender, since the risk are lower
    - „mini/allogeneic transplantation is a promising new approach“(?)
Current Paradigm of Initial Treatment

Transplant eligibility

Initial therapy

Transplant Candidates

Autotransplant

Consolidation

or

Maintenance

Non-transplant Candidates

Continue initial therapy
MM – SURVIVAL CURVES (Olomouc 1959 – 2011)  
(n-753)

- **1959-1963**: Sympt. therapy  
  (n-22, M-8)
- **1963-1975**: MP, CP  
  (n-67, M-19)
- **1976-1980**: VMP / VMCP, VBAP, VCAP  
  (n-108, M-40)
- **1981-1985**: VMCP, M-2, VAD  
  (n-57, M-34)
- **1986-1995**: KT / VAD, M-2, MP, NOP  
  (n-78, M-41)
- **1996-2007**: ASCT / IT (bez CTD / V-Dex)  
  (n-77, M-67)
- **1996-2011**: HDT / ASCT + TVR  
  (n-28, M-95)
- **1997-2011**: KT (VAD,MP,M2+TVR)  
  (n-26, M-74)
MAINTENANCE THERAPY

The role of anti-myeloma maintenance therapy following frontline therapy and ASCT is unclear

- continued alkylator therapy is not beneficial
- Several new agents are now being studied
  - THALIDOMIDE
  - REVLIMID (LEDALIDOMIDE)!
  - VELCADE (BORTEZOMIB)
  - vaccine approaches

No strong recommendation can be made for any particular maintenance strategy

- Lenalidomide (Revlimid) with or without steroids – is an option for maintenance, especially in high – risk settings
- Ledalidomid – is prefered in this time
Renal failure ("uraemia")
- rehydration and treatment of underlying cause (e.g. hypercalcaemia, hyperuricaemia)
- hemodialysis

Hypercalcaemia
- rehydration with isotonic saline
- corticosteroids intravenously
- bisphosphonates (pamidronate, zoledronic acid) intravenously
- active treatment of MM

Compression paraplegia
- HD-steroids (dexamethasone, methylprednisolone), chemotherapy
- X-ray irradiation
- decompression laminectomy
- vertebroplasty, kyphoplasty ("vertebral body reconstruction")

Single painful skeletal lesions
- X-ray irradiation + chemotherapy

Severe anaemia
- transfusion of packed red cells

Bleeding (MG interference with coagulation factors and HVS)
- repeated plasmapheresis
- coagulation factors substitution, etc.

Severe recurrent infections
- prophylactic infusions of immunoglobulin concentrates
- broad – spectrum antibiotics and antifugal agents
Kyphoplasty. The collapsing vertebral body is cannulated (a) so that an inflatable bone tamp can be placed at the site of compression (b). The tamp is then inflated (c), which restores vertebral body height. Finally, the cavity created by the tamp is filled with bone cement (d). Reproduced with permission from Dudeney et al. [25]
MM – supportive treatment

- **rHuEPO**
  - to improve the Hb level in persistent symptomatic anaemia (Hb < 100 g/l)
  - three times/week 10 000 IU s.c./titration of the dosis

- **BISPHOSPHONATES**
  - inhibit new bone destruction and improve of bone healing and recovery BMD
  - recommended for all myeloma related bone disease
  - pamidronate (Aredia), zoledronic acid (Zometa) and clodronate (Bonefos)

- **THE USE OF ANTIBIOTICS**
  - infections are common and recurrent
  - ATB – therapy should be instituted immediatelly if active infection is suspected
  - broad initial doverage is required

- **THE USE OF HD-GAMAGLOBULIN**
  - intravenous gamaglobulin may be a helpful – with acute and severe recurrent infections

- **G-CSF**
  - growth factor (G-CSF, Neupogen), in severe neutropenia in an effort to overcame infection complications

- **HAEMODIALYSIS**
  - in all patients with acute and chronic renal failure

- **PLASMAPHERESIS**
  - hyperviscosity syndrome (viscosity > 4)

- **RADIATION THERAPY**
  - pain control to allow ambulation and exercise
  - radiation and/or orthopedic surgery
    - to restore structural integrity of bones and recovery of full mobilization
  - radiation therapy for acute problems
    - spinal cord compression
    - severe refractory pain
    - treatment or prevent of pathological fracture

- **EXCERCISE**
  - walking and/or swimming is helpful to enhance bone strenght and remodeling
  - avoidance of risky activities