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MULTIPLE MYELOMA

PROPOSAL FOR DIAGNOSTIC AND THERAPEUTIC GUIDELINES

- ***Incidence of multiple myeloma***

Contemporary investigations reveal the increased annual incidence of multiple myeloma in Europe, from 3-4/100 000 to 6/100 000. The mean age of myeloma patients is 69 years, and only 5% of them are less than 40-year old.(1,2,3)

- ***Contemporary approach to diagnosis of multiple myeloma***

Diagnostic criteria

The diagnosis of multiple myeloma (MM) is based on the presence of minimum 1 "major" and 1 "minor" or minimum 3 "minor" criteria (4, Kyle/Greipp criteria):

≥ 1 "major" + 1 "minor"; or ≥ 3 "minor" criteria

Major	**Minor**
Plasmacytoma on tissue biopsy Marrow plasmacytosis ≥30%	Marrow plasmacytosis 10-29% in the bone marrow aspiration and/or biopsy
Monoclonal protein IgG > 35gr/L; IgA > 20gr/L; Bence Jones ≥1gr/24h	Monoclonal protein in lower concentrations than defined above
	Lytic bone lesions
	Hypogammaglobulinemia IgM < 0.5gr/L; IgA < 1gr/L; IgG < 6gr/L

The diagnosis can also be made based on the following criteria (4,5):

Symptomatic multiple myeloma*: All 3 criteria
1. 10% or greater marrow infiltration in the bone marrow aspiration and/or biopsy
2. Monoclonal protein in serum and/or urine[1]
3. Organ dysfunction caused by myeloma activity (≥1 criterion)[2]: **(C)** Elevated serum calcium (>10.5mg/l or > of the upper limit of the normal level) **(R)** Renal insufficiency (creatinine >177mmol/l) **(A)** Anaemia (hemoglobin levels lower than <10gr/dl or 2gr lower than normal values) **(B)** Osteolytic lesions or osteoporosis[3]

*These criteria define IB, II and III A and IIIB clinical stages of the disease (Durie&Salmon criteria). Thus the IA clinical stage (Durie&Salmon criterion) is equated with the so called "smouldering" or indolent myeloma.

[1]If monoclonal protein is not detected (nonsecretory disease), the criteria that are necessary to make the diagnosis are the marrow infiltration ≥ 30% or a plasmacytoma proven by the tumour tissue biopsy.

[2]Besides the aforementioned, diagnostic criteria may be organ dysfunctions associated with the MM activity, such as: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes within 12 months) requiring the commencement of the treatment.

[3]In case of a plasmacytoma proven by the tumour tissue biopsy or isolated osteoporosis without pathological fractures, the criterion necessary for making the diagnosis of MM is the marrow infiltration with plasma cells ≥ 30%.

Special entities, such as monoclonal gammopathy, indolent myeloma or solitary plasmacytoma are defined in accordance with the following criteria:

- **MGUS**: All 4 criteria have to be present

1. Monoclonal protein in serum and/or urine in low concentrations*
2. Marrow infiltration with plasmocytes <10%
3. Normal calcium, hemoglobin and creatinine levels
4. Absence of: a) osteolytic lesions of the skeleton as proven by radiographs of the skeleton and/or other radiographic methods; b) clinical and laboratory signs of amyloidosis/the disease which implies a variety of conditions in which light chains are deposited as well as other B cell lymphoproliferative diseases.

*The definition of the low concentration of paraprotein: In serum IgG<3.0gr/dl; IgA<2.0gr/dl; in the urine kappa/lambda<1.0gr/24h.

- **"Smouldering" or indolent myeloma***: All 3 criteria have to be present

1. Monoclonal protein in serum and/or urine
2. Marrow infiltration with monoclonal plasmocytes and/or a plasmacytoma proven by a biopsy
3. Absence of the criteria for MGUS, multiple myeloma or solitary osseous plasmacytoma and soft-tissue plasmacytoma

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*This defines the IA clinical stage of myeloma (Durie&Salmon criteria)

- **Solitary osseous plasmacytoma***: All 3 criteria have to be present
  1. Biopsy-proven isolated osseous plasmacytoma. Absence of other bone lesions proven by radiography of the skeleton, MRI and/or PET imaging. Association with low concentrations of monoclonal protein in serum and/or urine is possible.
  2. Marrow infiltration with monoclonal plasmocytes <10%.
  3. Absence of other signs of organ dysfunction related to the activity of multiple myeloma.

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*The definition of the low concentration of paraproteine: In serum IgG<3.0gr/dl; IgA<2.0gr/dl; in urine kappa/lambda<1.0gr/24h. (5, B.Durie et al. Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. The Hematology Journal, 2003, 4, 379-398).

Diagnostic methods

For the purpose of diagnosing multiple myeloma in compliance with the aforementioned clinical and laboratory criteria, it is necessary to perform a series of diagnostic tests comprising: Basic (Main) Diagnostics; Relevant Predictive Diagnostics; and Supplemental Diagnostics. (5,6)

Battery of basic diagnostic tests (5,6)

- Anamnesis (family anamnesis!) and physical findings
- Complete blood count test with leukocyte formula
- Complete analysis of the biohumoral status, including the determination of total protein, albumin, serum calcium level and lactate dehydrogenase (LDH)
- Serum protein electrophoresis and immunofixation*
- Non-felometric determination of immunoglobulin level*
- Routine analysis of urine and 24-hour urine immunofixation electrophoresis with quantification of monoclonal protein and albuminuria*
- Analysis and assessment of infiltration with pathological plasmocytes of the marrow aspiration and/or biopsy*
- Radiography of the scull, whole spine, chest, pelvis and other bones[1]
- Determination of beta-2-microglobulin concentration and the level of C reactive protein (CRP).

* In diagnostically unclear cases, the following has to be done:

a) Immunohystochemical analysis of the biopsy and/or immunophenotypization of the bone marrow aspirate for the purpose of proving the clonality of infiltration with plasmocytes

b) Quantitative assessment of free light chains in serum in case of suspected nonsecretory myeloma.

Relevant predictive diagnostics:

- Analysis of the conventional (metaphase) and interphase cytogenetics (FISH) in order to detect the presence of specific cytogenetic abnormalities:
  a) de1 13q14 [metaphase cytogenetics]
  b) del 17p; t(4;14); t(11;14); t(14;16) and t(6;14) [FISH]
- MRI of the axial skeleton in case of suspected solitary plasmacytoma or olygo-secretory meyloma

Supplemental diagnostics:

- Whole body PET scan for the purpose of excluding MGUS or extramedullary myeloma
- Biopsy of the subcutaneous fat tissue or the rectum in case of suspected amyloidosis
- Biopsy of the solitary osteolytic lesion
- Immunofixation for IgD or IgE paraprotein in case of negative immunofixation results for other types of paraprotein (5,6)

[1] Scintigraphy of the skeleton **IS NOT recommended** for the assessment of skeletal lesions in patients with multiple myeloma. In case of non-representative or negative radiographic findings and suspected bone lesions and/or extramedular disease and/or compression of the medulla spinalis it is necessary to examine the patient by CT scanning, PET/CT or magnetic resonance imaging (MRI). (7)

Indications for the assessment of the serum free light chain ratio

The assessment of the free light chain ratio in serum as the tumour mass parameter has 3 main applications:

1. Diagnostic criteria in case of myeloma of light chains, amyloidosis, oligo-secretory myeloma or suspected nonsecretory myeloma.
2. Assessment and follow-up of the treatment response of patients with immeasurable M component or olygo-secretory MM.
3. In monitoring patients in remission in case of suspected progression/relapse of the disease.
4. Prognostic significance in monitoring and detection of the progression of MGUS, asymptomatic myeloma, indolent or solitary plasmacytoma.

NOTE: The measureable M component is defined as: ≥10gr/l in serum or ≥200mg/24h in urine. In case of making a diagnosis of the plasma cell disorders, the assessment of the serum free light chains ratio CAN NOT REPLACE the analysis of 24h urine sample. (6,8)

Clinical stage and prognostic factors

The most frequently applied criteria for the assessment of the clinical stage of the disease are Durie-Salmon criteria as the tumour mass parameter (9):

Durie&Salmon criteria	**I stage** All mentioned below	**II stage** ≥ 1 criterion	**III stage** ≥ 1 criterion
Hemoglobin	> 100gr/l	85-100gr/l	< 85gr/l
Calcium	< 3mmol/l	< 3mmol/l	> 3mmol/l
M component IgA **IgG** **Light chains in urine**	 < 30gr/l < 50gr/l < 4gr/24h	 30-50gr/l 50-70gr/l 4-12gr/24h	 > 50gr/l > 70gr/l > 12gr/24h
X-ray skeleton	Normal	-	3 osteolytic changes
Sub-classification	A. creatinine < 177μmol/l B. creatinine > 177μmol/l		

In case of negative radiography result although there is suspected involvement of the skeleton, MRI or PET scan should be performed. The importance of these examinations is defined under Durie-Salmon plus classification that includes additional parameters of the unfavourable prognostic significance. (10,11,12)

***Durie-Salmon* PLUS classification**

Stage PLUS	MRI and/or FDG PET result
MGUS	Negative findings
MM IA (smouldering)	Solitary plasmacytoma or confined disease
MM IB	<5 focal lesions, mild propagation of the disease
MM IIA/B	5-20 focal lesions, moderate propagation of the disease
MM IIIA/B	>20 focal lesions, serious diffusive disease

A) Creatinine <2,0mg/dl[1];
Absence of extramedullary disease
B) Creatinine >2,0mg/dl[1];
Extramedullary disease

[1]Additional parameters of the negative prognostic significance are the following: Platelet count lower than 130x10e9/l, and/or elevated LDH.

Numerous multioptinal analyses of possible prognostic factors of multiple myeloma resulted in the creation of the international prognostic index - ***International Staging System (ISS)*** as the parameter of the activity of the disease, under which three prognostically significant groups of patients with myeloma are defined: those who are at low, moderate and high risk. (12)

International Staging System	**1** (low risk)	**2** (moderate risk)	**3** (high risk)
β2 microglobulin	< 3.5mg/l	< 3.5mg/l	> 5.5gr/l
Albumin	> 35gr/l	< 35gr/l	
		or β2 3.5-5.5mg/l	

Through the application of the **ISS** score patients with very poor prognosis and the life-expectancy rate of 12 - 24 months are defined as well as patients with very good life-expectancy rate that exceeds 5 years. Risk factors that are an additional indication of the aggressive course of the disease are the patients' old age, i.e. patients who are more than 60-year old, a low platelet count (below 130 x 10e9/l) and elevated LDH. On the other hand, the life-expectancy rate of more than 5 years is expected in patients who do not have the aforementioned risk factors, chromosome 13 deletion proven by conventional cytogenetics and/or complex cytogenetic abnormalities. (12)

Prognostic profile of patients with multiple myeloma

Through the application of the conventional cytogenetics, cytogenetic abnormalities are detected in one third of myeloma patients. Hypodiploid kariotype proven in this way and del13 are significant parameters of the unfavourable prognostic significance. Through the application of FISH, cytogenetic abnormalities are detected in more than 90% of myeloma patients. (6,8) Through the analysis of the prognostic significance of results determined by the conventional cytogenetics and 5 most frequent cytogenetic abnormalities proven by FISH, high-risk and low-risk patients with multiple myeloma are defined. (13,14)

1. High-risk patients (25%)
One of the following findings:

- t(4;14) – FISH
- t(14;16) or t(14;20) – FISH
- del17p13 – FISH
- Del13 or aneuploidy – metaphase cytogenetics

2. Low-risk patients (75%)
Absence of high-risk factors and presence of one of the following:

- Hyperdiploidy
- t(11;14) – FISH
- t(6;14) – FISH

Keeping in mind the prognostic significance and individual presence of specific cytogenetic abnormalities, the proposal of the panel of locus-specific FISH methods for the optimum diagnosis of MM is as follows: (13,14)

1. de1 13q14
2. del 17p
3. t(4;14)
4. t(11;14)
5. t(14;16)
6. t(6;14).

Treatment response assessment

High-dose chemotherapy with autologous hematopoietic stem cell (HSC) transplantation and introduction of new treatment modalities have resulted in defining complete and "stringent" complete remission as the highest level of the achieved treatment response. (15)

Treatment response criteria (International Myeloma Working Group uniform response criteria for multiple myeloma, 15**):**

1. **Stringent complete response (sCR) = CR PLUS**
    - Normal free light chains ratio in serum
    - Absence of monoclonal plasma cells in bone marrow, proven by immunohistochemistry or immunophenotypization

2. **Complete response (CR)**
- Absence of paraprotein in serum and/or 24h urine for 6 weeks
- Less than 5% plasma cells in the bone marrow aspiration and biopsy
- Normal calcium level
- Absence of radiographic signs of progression on the skeleton
- Absence of signs of so called extramedullary disease

3. **Very good partial response (VGPR)**
    - Paraprotein detectable by immunofixation but not on serum electrophoresis, or
    - Paraprotein reduction ≥90%, plus
      24-hour urine paraprotein level below 100mg per 24h

4. **Partial response (PR)**

- ≥ 50% reduction of serum paraprotein and serum free light chains maintained for 6 weeks
- ≥ 90% reduction of 24-h urinary paraprotein (<200mg per 24h) maintained for 6 weeks
- ≥ 50% reduction of bone marrow infiltration with plasmocytes in patients with nonsecretory myeloma
- Normal calcium level
- Absence of radiographic signs of progression on the skeleton
- ≥ 50% reduction of extramedullary disease

5. **Stable disease (SD)**

- Oscillating serum paraprotein ±25% for 3 months
- Oscillating of 24-h urinary paraprotein ±25% for 3 months
- Absence of radiographic signs of progression of changes in the skeleton for 3 months

5. **Disease progression - relapse (PD)**

Presence of one of the following criteria confirmed in 2 subsequent test results within 4 weeks:

- Elevated paraprotein or serum free light chains by more than 25%
- Elevated urinary paraprotein by more than 25%
- Bone marrow infiltration with pathological plasma cells ≥ 10%
- Hypercalcemia (above 2.65mmol/l)
- Appearance of new changes in the skeleton or an increase in the size of the initial ones ≥50% cross-section
- In patients with nonsecretory myeloma: An increase in the number and size of osseous changes; Elevated calcium level; increased bone marrow infiltration with plasma cells and/or elevated β2 microglobulin ≥ 50% as compared to the initial value

NOTE: The normal ratio of kappa (3.3-19.4mg/l) and lambda (5.7-26.3mg/l) serum light chains ranges from 0.26 to 1.65. Patients with κ/λ <0.26 are featured by monoclonal λ paraprotein, while κ paraproteinemia is defined by κ/λ >1.65.

Additional treatment response criteria (16):

- **Relapsing myeloma:** Patient have been previously treated with minimum one line of treatment.
- **Relapsing and refractory myeloma:** Progression of the disease has occurred during the "salvage" therapy or within the first 60 days after the last line of treatment.
- **Minimal response (MR) of patients with relapsing/refractory myeloma:**
    - **a)** Reduced serum M protein by 25-49%
    - **b)** Reduced 24-h urinary paraprotein by 50-89% with persistent 24-h proteinuria above 200mg/24h
    - **c)** Reduced size of extramedullay plasmacytoma by 25-49%
    - **d)** Absence of radiographic signs of progression on the skeleton
- **Progression of indolent myeloma into active multiple myeloma:** Progression of the disease in accordance with the IMWG criteria and minimum one of the following criteria:

a) Appearance of new soft tissue infiltrates or bone lesions

b) Hypercalcemia (>2.65mmol/l)

c) Drop down in hemoglobin by minimum 2gr/100ml

d) Elevated creatinine level of more than 177μmol/l.

- **<u>Prognostic significance of the response to treatment</u>**

The therapeutical guidelines for the contemporary treatment of multiple myeloma are based on the analysis of the patient's prognostic profile, the treatment approach adapted to individual patient requirements and the assessment of the level and duration of the treatment response (17):

1. **<u>Objective of the contemporary treatment</u>: To achieve a CR – this is <u>essentially important</u> for the course of the disease and life-expectancy duration!**

2. **<u>Prognostic significance of duration of the positive treatment response:</u>**

    - **Early relapse (remission less than 1 year) – HIGH-RISK PATIENTS = THE TREATMENT HAS TO BE INTENSIFIED**
    - **Intermediate – average relapse (remission of 1-3 years) = Sequential application of NEW treatment modalities**
    - **Late relapse (remission for more than 3 years) = REINDUCTION OF THE INITIAL treatment OR a combination based on the application of NEW treatment modalities, WITH THE CONTINUED TREATMENT with high-dose chemotherapy and autologuos HSC transplantation (AUTOSCT).**

- ***Treatment of patients with multiple myeloma***

The decision on the initial treatment for each individual patient depends on the following:

- Stage of the disease
- Clinical presentation of the disease (indolent, systemic myeloma or extramedullary presentation)
- Patient's age, i.e. ability to be treated with high-dose chemotherapy
- Presence of renal insufficiency
- Patient's general condition
- Associated comorbidities (cardiovascular diseases, diabetes, thrombophilia or other trombogenic conditions)
- Prognostic profile.

Depending on these criteria, the treatment objective has to be defined for each individual patient as well as a concrete approach to treatment.

1. **Newly diagnosed patients in the IA clinical stage (Durie&Salmon)**

Patients in the IA clinical stage without any symptoms do not require any specific hematology treatment. These patients should be followed up with regard to their hematological status in three-month intervals. (3)

2. **Newly diagnosed patients who are less than 65-year old**

The final objective of the treatment of these patients is to achieve long-lasting remission (>10 years) and potential recovery (17):

- **II and III clinical stage (< 65 years)**
- Chemotherapy in combination with thalidomide (CTD or TAD)

OR

- Chemotherapy in combination with bortezomib (Vel-Dex, PAD or VTD)

NOTE: The selection of the treatment shall depend on the individual profile of each patient: Presence of a renal impairment, general condition, presence of cardiovascular diseases, diabetes, thrombophilia and other thrombogenic conditions, specific cytogenetic abnormalities, extramedular type of the disease.

3) In patients who are less than 65-year old, without renal function damage, after the 4th cycle of induction therapy and achieved partial remission (PR), the treatment should be continued with high-dose chemotherapy and autoSCT.

4) In patients with a renal impairment that does not require hemodialisis, who are less than 50-year old and in good general condition, after the 4th cycle of induction therapy and achieved partial remission, the treatment may be continued with high-dose chemotherapy reduced by 50%.

5) Patients with renal insufficiency requiring hemodialisis may be treated by high-doses of Dexamethasone, 2 cycles + treatment in accordance with the Guidelines 1, 2, 3 and 4, depending on the recovery of renal insufficiency. (3,17,18,19,20,21,22,23)

6) Mobilization with apheresis and cryopreservation ≥5x10e6/kg BW CD34+/HSC from peripheral blood should be conducted for 3-5 weeks after the 3rd-4th cycle of induction treatment, by applying the mobilization protocol CAD with G-CSF. (20,21,22)

7) High-dose chemotherapy as per protocol Melphalan 200mg/m2 followed up by autoSCT from peripheral blood should be conducted for 3-5 weeks after the mobilization and apheresis of HSC. The treatment response assessment should be conducted on +100th day after the autologuous transplantation. (20,21,22)

8) Tandem autoSCT is conducted in case of the achieved PR as the maximum response, on +100th day from the first autologous transplantation. Optimally, tandem autoSCT is conducted in the first 3-12 months after the first transplantation.(17,18,19,20,23)

3. <u>Newly diagnosed patients who are more than 65-year old</u>

The objective of the treatment of these patients is to prolong their survival, with the maintenance of good general condition, and to reduce as much as possible the necessity of being hospitalized. (17)

- **<u>II and III clinical stage (> 65 years)</u>**
- Chemotherapy in combination with thalidomide (MPT or CTD)

<u>OR</u>

- Chemotherapy in combination with bortezomib (MPV, Vel-Dex or VTD)

NOTE: The selection of the treatment depends on the individual profile of each patient: presence of a renal impairment, general condition, presence of cardiovascular diseases, diabetes, thrombophilia and other thrombogenic conditions, specific cytogenetic abnormalities, extramedullary presentation of the disease.

3) Patients who are more than 65-year old and who have renal insufficiency that requires hemodialisis may be treated with high doses of Dexamethasone, 2 cycles + treatment in accordance with the aforementioned items 1 and 2, depending on the recovery of the renal function. (17,18,19,20)

Treatment response monitoring

In case of a favourable treatment response and/or progression of the disease after the 2nd fully completed cycle of chemotherapy, the continuation of the treatment by applying another line of treatment is indicated.

Specificities of the treatment with thalidomide and bortezomib:

A. **Chemotherapy in combination with thalidomide and dexametasone:**

   Anticoagulant prophylaxis (low-molecular-weight-heparin and/or peroral anticoagulation therapy) during first 4-6 months of treatment.

B. **MPT combination or monotreatment with thalidomide:**

   Antiaggregation prophylaxis with aspirin (100mg per day p.o.) in case of any other risk factors for thrombosis.

C. **Positive personal anamnesis with regard to previous thrombosis:**

   Hemostatic and genetic examination for thrombophilia. In patients with thrombophilia the treatment without thalidomide is recommended. (7,18)

D. Renal function insufficiency (creatinine > 300mmol/l):

Potassium levels should be monitored. In case of persistent hyperkalemia, thalidomide has to be withdrawn. (17,18,19,20,24,25)

E. Occurrence of polyneuropathy during treatment:

- Polyneuropathy NCI CTC grade 1+pain or 2, reduction of the thalidomide dose (100mg per day p.o.) or bortezomib (1.0mg/m²).
- Polyneuropathy grade 2+pain or 3: Withdrawal of thalidomide; Delayed administration of bortezomib until symptoms are withdrawn, and after that the administration of the reduced dose 0.7mg/m² 1x per week.
- Polyneuropathy grade 4: Withdrawal of bortezomib. (25)

F. Chemotherapy in combination with bortezomib

- Necessary antiviral prophylaxis of HZV infection. (25,26,27)

Maintenance treatment

Achieved partial response: Thalidomide 50-100mg per day p.o. during one year period.

- Alfa-Interferon maintenance (3MU 3x weekly) can be applied in the case of contraindications or adverse events of thalidomide. (3,17)

Treatment of patients with relapsing multiple myeloma

Patients with relapsing multiple myeloma may be classified into three groups:

- Early relapse (remission less than 1 year)
- Intermediate relapse (remission of 1-3 years)
- Late relapse (remission of more than 3 years).

1. **Early relapse (remission < 1 year) and patients < 65-year old:** Intensive chemotherapy protocols with bortezomib (PAD, VDT-PACE) or TCED in patients who were not initially treated with thalidomide.

2. **Intermediate relapse (remission of 1-3 years) and patients ≥ 65-year old:**

   Moderate intensity chemotherapy combinations with bortezomib (MPV, Bortezomib-Dexamethason) or CTD in patients who were not initially treated with thalidomide.

3. **Late relapse (remission > 3 years):**
   - To repeat the initial induction treatment
   - Chemotherapy in combination with bortezomib or thalidomide in patients to whom it has not been initially administered.

NOTE:

- In patients who are relapsing for the first or second time, the treatment in compliance with sections 1, 2 and 3 should be applied.
- After achieving complete/partial remission, apply thalidomide as the maintenance therapy. In patients who are < 65-year old, the possibility of autologous and/or allogenic SCT should be taken into consideration with reduced-intensity conditioning regimes. (3,17,26,27)

8. Treatment of primary refractory patients

- Primary resistant non-progressive patients after induction treatment may be treated by tandem high dose chemotherapy followed up by autoSCT.
- Primary resistant progressive patients may be treated with new treatment modalities within clinical trials.(17)

9. Palliative treatment

After the second and/or subsequent relapses palliative treatment may be applied: Cyclophosphamide 50mg/II day p.o. or prednisone 30mg/II day p.o, if the patient is not eligible for further intensive hematological treatment.(3,17,26,27)

Hypercalcemia and bone disease

- **Hypercalcemia**

Hypercalcemia occurs in 30% patients suffering from multiple myeloma and the signs of active/progression of the disease are the following:

a) Mild hypercalcemia (2.6-2.9mmol/l): Rehydratation.

b) Moderate-severe hypercalcemia (calcium > 2.9mmol/l):

1) Rehydratation; 2) Osmotic diuretics and/or furosemide (80-100mg per day); 3) **Immediate** administration of bisphosphonate (zolendronat 4mg i.v. in 15min infusion; pamidronate 90mg i.v. in 4h infusion); 4) calcitonin.

c) When there is an impairment of renal function: 1) The administration of zolendronat in not recommended in case of creatinine > 300mmol/l; 2) the duration of the pamidronate infusion is extended to more than 4h; 3) concurrent application of nephrotoxic drugs should be avoided (non-steroid antireumatic drugs, aminoglycosides, contrasting agents). (3,7,28,29)

- **Multiple skeletal lesions**

Skeletal lesions occur in 90% patients with multiple myeloma.

a) Treatment approach to patients with bone lesions implies local radiation treatment (8-30Gy) and orthopedic interventions (kyphoplasty and vertebroplasty) and long-time administration of bisphosphonate: zolendronat (4mg i.v. in 5-15min infusion, in four-week cycles)*; or pamidronate (90mg i.v. in 2-4h infusion, in four-week cycles); or clodronate (1600mg per day p.o.).

b) Indications for the administration of bisphosphonate: Patients at Stage III with distinct bone lesions and/or progression of the disease in the form of new pathological fractures.

c) Treatment choice between the said bisphosphonate depends on the discretion of the doctor and the patient.

d) Duration of application: 1) Optimum – one year of treatment; 2) Maximum – during two years of treatment.

*Application of zolendronat requires: a) Creatinine level monitoring. In case of creatinine >265micromol/l, the administration of zolendronat is not recommended. b) Calcium supplements (500mg per day p.o.) and vitamin D (400IU per day p.o).(3,7,28,29).

Appendix

Chemotherapy in combination with thalidomide and high doses of Dexamethasone	**Chemotherapy in combination with bortezomib**
CTD Cyclophosphamide 500mg i.v. 1st; 8th; 15th day. Thalidomide 100-200mg per day p.o. Dexamethasone 40mg per day i.v. 1st-4th; 12th-15th day. * 4-6 three-week cycles.	**MPV** Melphalan 9mg/m² per day p.o. 1st-4th day. Prednisone 60mg/m² per day p.o. 1st-4th day. Bortezomib 1,3mg/m² i.v. 1st; 4th; 8th; 11th; 22nd; 25th; 29th; and 32nd day. * 4 six-week cycles.
TAD Thalidomide 100-200mg per day p.o. Doxorubicin 9mg/m² i.v. in 30min infussion 1st-4th day Dexamethasone 40mg/dan i.v. 1st-4th; 9th-12th; 17th-20th day. * 4-6 four-week cycles.	**Vel-Dex** Bortezomib 1,3mg/m² 1st; 4th; 8th; 11th day. Dexamethasone 20mg i.v. 1st; 2nd; 4th; 5th; 8th; 9th; 11th; and 12th day. * 8 three-week cycles.
Thal-Dex Thalidomide 100-200mg per day p.o. Dexamethasone 40mg i.v. 1st; 8th; 15th; 22th day. * 12 four-week cycles.	**PAD** Bortezomib 1,3mg/m² i.v. 1st; 4th; 8th; 11th day. Doxorubicin 9mg/m² i.v. in 30min. infussion 1st-4th day. Dexamethasone 40mg/dan i.v. 1st-4th; 9th-12th; and 17th-20th days. * 4-8 four-week cycles.
MPT Melphalan 4mg/m² per day p.o. for 7 days Prednisone 40mg/m² per day p.o. for 7 days Thalidomide 100mg per day p.o. * 6 four-week cycles.	**VTD** Bortezomib 1,3mg/m² i.v. 1st; 4th; 8th; 11th day. Thalidomid 200mg per day p.o. Dexamethasone 40mg per day i.v. 1st; 2nd; 4th; 5th; 8th; 9th; 11th; 12th day. * 3 three-week cycles prior to autoSCT .
TCED Thalidomide 100-200mg per day p.o. Cyclophosphamide 400mg/m² per day i.v. cont. 1st-4th day. Etoposide 40mg/m² per day i.v. cont. 1st-4th day. Dexamethasone 40mg per day i.v. 1st-4th day. * 6 four-week cycles.	**VDT-PACE** Bortezomib 1,0mg/m² i.v. 1st; 4th; 8th; and 11th day Dexamethasone 40mg per day i.v. 1st-4th day. Thalidomide 200mg per day p.o. 4th-7th day. Cisplatinum 10mg/m² per day i.v. cont. 1st-4th day. Doxorubicin 9mg/m² per day i.v. cont. 1st-4th day. Cyclophosphamide 400mg/m²/day i.v. cont. 1st-4th day. Etoposide 40mg/m² per day i.v. cont. 1st-4th day. G-CSF 5µgr/kg BW per day s.c. starting from the 7th day until recovery. * 2 six-week cycles.
High doses of Dexamethasone Dexamethasone 40mg per day i.v. 1st-4th; 9th-12th; 17th-20th day. * 2-6 four-week cycles.	

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