Multiple myeloma (Plasma Cell Myeloma)

Status: June 2019

Multiple myeloma (MM), also known as plasma cell myeloma, can be classified within plasma cell neoplasm. In addition to classification and diagnostics, we will also present therapy options and prognoses for multiple myeloma.

Diagnostic recommendation

<table>
<thead>
<tr>
<th>Method</th>
<th>Anticoagulant</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyto morphology</td>
<td>EDTA</td>
<td>mandatory</td>
</tr>
<tr>
<td>Immuno phenotyping</td>
<td>EDTA or Heparin</td>
<td>optional</td>
</tr>
<tr>
<td>Chromosome analysis</td>
<td>Heparin</td>
<td>no</td>
</tr>
<tr>
<td>FISH</td>
<td>EDTA or Heparin</td>
<td>mandatory</td>
</tr>
<tr>
<td>Molecular genetics</td>
<td>EDTA or Heparin</td>
<td>optional</td>
</tr>
<tr>
<td>Histology</td>
<td>Formalin</td>
<td>mandatory</td>
</tr>
</tbody>
</table>
Multiple Myeloma - Definition and characteristics

Plasma cell myeloma (according to WHO) or multiple myeloma (MM) is characterized by a malignant plasma cell proliferation in the bone marrow and is accompanied by an increased production of monoclonal immunoglobulins, which are usually detectable in serum as M-gradients.

The diagnosis of suspected or confirmed multiple myeloma is complex and includes not only cytomorphology but also histology, imaging techniques, serum and urine tests such as immunofixation or immunoelectrophoresis and determination of the light chains of immunoglobulins. In addition, genetic methods - currently primarily FISH analysis of cell fractions previously enriched by separation to 2013B positive plasma cells - are of great importance for prognostic classification. Immunophenotyping can also provide valuable information in many cases, since it can detect aberrant expression patterns on the plasma cells, and thus monoclonality, with high sensitivity. It is the most important technique for MRD. Molecular genetic studies are gaining increasing importance with regard to additional prognostic information (e.g., TP53 mutation) or the use of targeted therapies (e.g., BRAF mutation).

Classification of the Multiple Myeloma

According to the WHO classification 2017, multiple myeloma belongs to the group of plasma cell neoplasms within mature B-cell neoplasms. The diagnosis of suspected or confirmed multiple myeloma is complex and includes not only cytomorphology but also histology, imaging techniques, serum and urine tests such as immunofixation or immunoelectrophoresis and determination of the light chains of immunoglobulins. In addition, genetic methods - currently primarily FISH analysis of cell fractions previously enriched by separation to 2013B positive plasma cells - are of great importance for prognostic classification. Immunophenotyping can also provide valuable information in many cases, since it can detect aberrant expression patterns on the plasma cells, and thus monoclonality, with high sensitivity. It is the most important technique for MRD. Molecular genetic studies are gaining increasing importance with regard to additional prognostic information (e.g., TP53 mutation) or the use of targeted therapies (e.g., BRAF mutation).

Multiple Myeloma WHO-Classification 2017
(Swerdlow et al. 2017)

Mature B-cell neoplasm

• Plasma cell neoplasms
  - Plasma cell myeloma (multiple myeloma)

Depending on the concentration of the M protein in the serum and the proportion of plasma cells in the bone marrow, the asymptomatic phases "monoclonal gammopathy of undetermined significance" (MGUS) and "smoldering multiple myeloma" (SMM) are distinguished. A transition to symptomatic myeloma occurs in patients with MGUS with a probability of approximately 1% per year, while the risk of progression in patients with SMM is 10% per year in the first 5 years.

Risk classification according to International Staging System (ISS), lactate dehydrogenase and FISH

To identify the risk group, a combination of the International Staging System (ISS; see Table 1), lactate dehydrogenase in serum and cytogenetics using FISH is recommended (Moreau et al. 2017). For cytogenetic diagnostics, the International Myeloma Working Group recommends at least the performance of FISH analyses for the detection of the 1p deletion and the translocation t(4;14). Analyses for the detection of 1q gains and 1p deletions as well as t(14;16) and t(14;20) represent a useful extension for risk stratification (Sonneveld et al. 2016).

Table 1: International Staging System and risk factors (ESMO-Guidelines: Moreau et al. 2017)

<table>
<thead>
<tr>
<th>International Staging System (ISS) (P. Greipp et al. 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
</tbody>
</table>

β2M = β2 microglobulin, LDH = lactat dehydrogenase, ULN = upper limit of normal

Previous risk stratification models only consider the detection of certain aberrations, but not their interaction. A recently developed weighted index integrating six prognostically relevant changes ([t(4;14), del(17p)], trisomy 5, trisomy 21, 1q gain, del(1p32)] achieved a higher prediction accuracy than the ISS (Peret al. 2019) and shows potential for improvement of the previous risk stratifications.

In addition, it was shown that gene expression analyses are of high prognostic relevance for patients with multiple myeloma and that the combination of gene expression profiles with the ISS represents a significant prognostic factor (Shaughnessy et al. 2007, Kuiper et al. 2015). In the foreseeable future, molecular markers will also become routine; BRAF mutations already have therapeutic relevance.

Facts

25% of MM-patients have no symptoms at diagnosis

(Oncpedia guideline multiple myeloma)

Multiple Myeloma - Diagnostics
Cytomorphology

Important for the differentiation of multiple myeloma, MGUS and SMM

The cytomorphological examination of bone marrow aspirates or biopsies for plasma cell infiltration is performed as standard to assess the number and characteristics of plasma cells in the bone marrow. This serves primarily to distinguish multiple myeloma from MGUS and SMM (see Table 2).

Table 2: Diagnostic criteria to distinguish MM, MGUS and SMM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of plasma cells in BM</td>
<td>&lt; 10%</td>
<td>≥ 10%</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>End-organ damage*</td>
<td>non</td>
<td>non</td>
<td>existing</td>
</tr>
</tbody>
</table>

*CRAB criteria: Hypercalcemia, renal failure, anemia, bone lesions

The determination of the plasma cell fraction has not only diagnostic but also therapeutic relevance. For example, a proportion of clonal plasma cells in the bone marrow of ≥ 60% is one of three criteria that determine the therapeutic indication even in the absence of end organ damage (SLI criteria of the International Myeloma Working Group (Rajkumar et al. 2014)).

Immunophenotyping

If a paraprotein is detected or if multiple myeloma is clinically suspected, immunophenotyping can be used to complement other methods (immunohistology). Immunophenotyping is also helpful for the diagnosis, the course of disease after multiple myeloma therapy and is increasingly established for the determination of measurable residual disease (MRD). It is being discussed or already used as an endpoint in studies (Mateos et al. 2018).

CD45, CD19, CD56 and CD138 are relevant surface markers in MM

Malignant plasma cells often show reduced or absent expression of the pan-leukocyte antigen CD45 and the B-cell marker CD19 compared to healthy polyclonal plasma cells, and in many cases aberrant expression of the antigen CD56, which is normally not expressed relevantly on plasma cells. They show a specific light chain restriction.

Differentiation from MGUS and assignment of the plasma cell population

At the cytoplastic level, the detection of a light chain restriction is possible. Thus, immunophenotyping helps to distinguish benign plasma cell proliferation from plasma cell dyscrasia (MM or MGUS). In bone marrow aspirates with cytomorphologically limited assessment or in multiple myeloma with extremely atypical plasma cells in cytology, immunophenotyping allows a clear assignment of the plasma cell population. Furthermore, immunophenotyping can help to differentiate paraproteinemias of unclear genesis from other B-cell lymphomas.

Chromosome analysis

Aberrant plasma cells difficult to detect by chromosome analysis

In classical chromosome analysis, aberrant plasma cells are usually not detected in vitro due to their low proliferation activity. FISH analysis on interphase nuclei is therefore of central importance in multiple myeloma. After enrichment by magnet-activated cell sorting (MACS) for CD138+ plasma cells, a purity level of plasma cells of mostly ≥ 80% is achieved even in MGUS, even if the infiltration level in native bone marrow is much lower. The enrichment of CD138+ cells by FISH allows the detection of chromosomal changes in 90% of all multiple myelomas with proof of monoclonality, but more importantly: with relevant prognostic impact.

Fluoreszenz in situ Hybridisierung (FISH)

Differentiation of hyperdiploid and non-hyperdiploid multiple myeloma

FISH analysis is particularly important in multiple myeloma. Using FISH, chromosomal changes were detected in 88-97% of all cases. Cytogenetically, the hyperdiploid group can be distinguished from the non-hyperdiploid group (Sawyer et al. 2019).

Cytogenetic classification of multiple myeloma (International Myeloma Working Group, IMWG):

- Hyperdiploid MM
  - 50-60% of patients
  - multiple trisomies, especially of chromosomes 3, 5, 7, 9, 11, 15, 19 and 21
  - Association with a more favourable prognosis

- Non-hyperdiploid MM
  - approx. 30% of patients
  - hypodiploid/pseudodiploid chromosome sets
  - high incidence of translocations involving the IGH locus
  - Monosomies, especially chromosomes 13, 14, 16 and 22
  - heterogeneous courses, prognosis depending on the specific IGH rearrangement (see Table 3)

- MM with multiple trisomies and a translocation involving the IGH locus
Prognosis

14-20%
11-15%
Incidence
1-2%

In the literature, there is controversial discussion whether gains are associated with disease progression and a shorter survival time (Aivet-Laizeau et al., 2012, Shah et al., 2018, Perrot et al., 2019). In the literature, there is controversial discussion whether gains are associated with disease progression and a shorter survival time (Aivet-Laizeau et al., 2012, Shah et al., 2018, Perrot et al., 2019). In the literature, there is controversial discussion whether gains are associated with disease progression and a shorter survival time (Aivet-Laizeau et al., 2012, Shah et al., 2018, Perrot et al., 2019).

Other structural aberrations that are common in myeloma are gains of 1q and 11q, deletions of 1p, 6q, 8p, 13q, 14q, 16q, and 17p, and MYC rearrangements.

Molecular genetics

Mutations often affect MEK/ERK and NFκB signalling pathways

Over 50% of patients with multiple myeloma have a mutation in one component of the MEK/ERK pathway. Thus, NRAS and KRAS mutations are found in 19-21% and 21-27% of patients, respectively, and BRAF mutations in 4-7%, whereby these mutations are almost mutually exclusive and occur together in only about 2% of patients (Chapman et al., 2011, Walker et al., 2015).

Furthermore, about 17% of patients show mutations affecting the NFκB signalling pathway (e.g., in the genes TRAF3 and CYLD). Mutations in the TP53 gene, which occur in 3-8% of patients, are associated with del(7q) and an unfavourable prognosis. According to one study, the latter also applies to mutations in CCND1, ATM, and FDR, while IRF4 and EGR1 mutations correlate with prolonged survival (Walker et al., 2015). Furthermore, recurrent mutations and deletions are found, for example, in other tumour suppressor genes such as FAM46C, DIS3 and RB1, as well as in the genes PDGFRα and JAK3 coding for receptor tyrosine kinases (Chapman et al., 2011, Mulligan et al., 2014, Balli et al., 2014, Walker et al., 2015). In patients with a t(11;14) a significant occurrence of CCND1 mutations has been described, while patients with a hyperdiploid karyotype have frequent mutations in the EGR1 gene (Walker et al., 2015).

Molecular genetic diagnostics support the prognostic assessment by genetic characterization of multiple myeloma and determination of clonal heterogeneity and minimal residual disease (Lonetti & Neri, 2017). With the progressive development of targeted agents, therapeutic benefit is expected to increase in the future (Pawlyn & Davies, 2019).

Multiple Myeloma - Prognosis

Multiple myeloma with hyperdiploidy is the most prognostically favorable subtype

The favourable prognosis for patients with multiple myeloma with a hyperdiploid set of chromosomes has recently been confirmed. Thus, a clear advantage in survival analysis was shown for this MM subtype compared to all other cytogenetic subgroups. Even for patients with the translocation t(11;14)(q13;q32), which is also assigned to the standard risk group, a less favourable prognosis was shown than for patients with hyperdiploidy (Lashkin et al., 2018, Shah et al., 2018).

IGH rearrangements have different prognostic significance

The most frequent translocation partners of the IGH locus in multiple myeloma are CCND1, FGFR3 (4p16), MAF (6q23), MAFB (20q12) and CCND3 (6p21). Table 3 shows the prognostic significance of the various IGH rearrangements.

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Prognosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)(p16;q32)</td>
<td>poor</td>
<td>11-15%</td>
</tr>
<tr>
<td>IGH-CCND3-rearrangement</td>
<td>poor</td>
<td>3-6%</td>
</tr>
<tr>
<td>t(14;16)(p13;q23)</td>
<td>poor</td>
<td>1-2%</td>
</tr>
<tr>
<td>IGH-MAF-rearrangement</td>
<td>favorable</td>
<td>14-20%</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>IGH-CCND3-rearrangement</td>
<td>favorable</td>
</tr>
</tbody>
</table>

(Bacher et al., 2010, Sawyer et al., 2011, Morgan et al., 2012, Sonneveld et al., 2016).

Prognosis of frequent structural aberrations: Gains, deletions and MYC rearrangements

The prognostic significance of the most frequent structural aberrations is summarized in Table 4.

Gains

1q Gains are associated with disease progression and a shorter survival time (Aivet-Laizeau et al., 2012, Shah et al., 2018, Perrot et al., 2019). In the literature, there is controversial discussion whether 1q amplification additionally worsens the prognosis (Walker et al., 2015, Shah et al., 2018, Perrot et al., 2019). The definition of the number of copies from which amplification is present differs between the sources - which further limits the comparability of the studies. Since even high-dose therapy protocols and/or drugs of new substance classes do not improve the prognosis for 1q gains, a therapy approach similar to that for patients with a different high-risk aberration should be considered for these patients (Kumar & Rajkumar, 2018).

Deletions

1p deletions are associated with an unfavourable prognosis, whereby the prognosis is more unfavourable for a 1p32 region deletion than for a 1p22 region deletion (Hebraud et al., 2013 and 2015, Shah et al., 2018, Perrot et al., 2019).
The published association of 13q deletions detected by FISH with an unfavorable prognosis is based on the abundance of the region together with the unfavorable aberrations (t(4;14) and del(13q) (Fonseca et al. 2009, Neben et al. 2010 and 2012). In contrast, del(13q) detected by conventional chromosome analysis is associated with a less favorable prognosis (Chiecchio et al. 2006).

17p deletions are associated with an unfavorable prognosis (An et al. 2015, Shah et al. 2018, Perrot et al. 2019), whereby it is discussed from which clone size on the negative influence becomes effective (An et al. 2015). 17p deletions may also include the TP53 gene. If a biallelic TP53 inactivation results from a deletion or mutation of the second allele, this further worsens survival (Weinhold et al. 2016, Walker et al. 2018 and 2019, Thakurta et al. 2019).
MYC rearrangements and amplifications

Rearrangements and amplifications of the MYC gene usually occur at a later stage and are associated with an unfavourable prognosis - this alteration is observed in approximately 45% of patients with advanced multiple myeloma (Morgan et al., 2012, Walker et al., 2014).

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Prognosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q gain</td>
<td>poor</td>
<td>36-49%</td>
</tr>
<tr>
<td>1p deletion</td>
<td>poor</td>
<td>30%</td>
</tr>
<tr>
<td>13q deletion</td>
<td>-</td>
<td>45-58%</td>
</tr>
<tr>
<td>17p deletion</td>
<td>poor</td>
<td>7-13%</td>
</tr>
<tr>
<td>MYC rearrangement</td>
<td>poor</td>
<td>5-15%</td>
</tr>
<tr>
<td>6q deletion</td>
<td>favor</td>
<td>24%</td>
</tr>
<tr>
<td>8p deletion</td>
<td>-</td>
<td>23-25%</td>
</tr>
<tr>
<td>11q gain</td>
<td>-</td>
<td>2%</td>
</tr>
<tr>
<td>12p deletion</td>
<td>poor</td>
<td>15%</td>
</tr>
<tr>
<td>16q deletion</td>
<td>poor</td>
<td>20-35%</td>
</tr>
</tbody>
</table>

(Munshi et al., 2011, Avet-Loiseau et al., 2011, Morgan et al., 2012, Neben et al., 2012, Avet-Loiseau et al., 2013, An et al., 2015)

Prognostic relevance of trisomies in high risk aberrations unclear

Whether the presence of trisomies improves the prognosis of patients with simultaneous 1p deletion, t(4;14), t(14;16) or t(14;20) is controversially discussed. The contradictory results are probably due, among other things, to the different treatment protocols used in the studies (Kumar et al., 2012, Pawlyn et al., 2015). In addition, a divergent prognostic effect was described for individual trisomies. While trisomies of chromosomes 3 and 5 have a positive influence on survival, trisomy 21 leads to a worsening of the prognosis (Chieffo et al., 2015, Petr et al., 2019).

Combined occurrence of unfavourable aberrations worsens prognosis

According to Sonneveld et al., prognostically unfavorable aberrations include the translocations t(4;14), t(14;16), t(14;20), the 1q gain and the 17p deletion (Sonneveld et al., 2018). If t(4;14) or del(17p) occurs, the prognosis worsens regardless of the ISS stage (Avet-Loiseau et al., 2013).

For the aberrations mentioned above, it has been shown that the negative influence on the course of the disease is less when they occur alone than when several of these aberrations occur simultaneously (Boyd et al., 2012, Shah et al., 2018).

Shah et al. speak in this context of the "double-hit". Table 5 shows the survival as a function of the number (0-2) of prognostically unfavorable aberrations for MM patients in the Myeloma XI study. While three unfavorable aberrations were detected, median overall survival was only 19 months (Shah et al., 2018).

Table 5: Survival of patients with multiple myeloma according to number of prognostically unfavorable aberrations (t(4;14), t(14;16), t(14;20), 1q gain, del(17p)) in a myeloma XI study cohort (Shah et al., 2018)

<table>
<thead>
<tr>
<th>Survival analysis of 1036 MM patients of the Myeloma XI study</th>
<th>No adverse lesions</th>
<th>One adverse lesion</th>
<th>Double-hit (two adverse lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progression free survival</td>
<td>31.1 months</td>
<td>24.2 months</td>
<td>17 months</td>
</tr>
<tr>
<td>Median overall survival after 24 months</td>
<td>86.4%</td>
<td>76.6%</td>
<td>66.1%</td>
</tr>
</tbody>
</table>

(Munshi et al., 2017, Flores-Mantero et al., 2017, Kumar & Rajkumar, 2018). Imaging techniques can be used, MRD negativity is associated with longer survival (PFS and OS) (Munshi et al., 2017, Lahuerta et al., 2017). Despite its prognostic significance, MRD diagnosis in multiple myeloma has
no clinical relevance to date - however, the use of MRD detection for therapy control is under discussion (Kumar & Rajkumar 2018). It will be in use for endpoint control in studies testing new drugs.

When relapses occur, the duration of the response to the initial therapy, especially after autologous stem cell transplantation (ASCT), is an important prognostic factor. If recurrences occur early (12-18 months after ASCT), this is associated with an unfavourable prognosis – even if other high-risk factors are missing (Kumar & Rajkumar 2018).

Multiple Myeloma (MM): Prognosis calculation
Here you can access the prognostic calculation of the ISS score and the R-ISS score.

Multiple Myeloma - Therapy

Plasma cell myeloma: Therapy protocols with bortezomib improve prognosis in (6;14) patients
Overall, new therapeutic developments have repeatedly significantly improved the prognosis of patients with multiple myeloma, with the introduction of proteasome inhibitors and immunomodulators alone increasing median survival by 4.7 years (Tonseca et al. 2017).

The therapeutic agents currently approved for the treatment of multiple myeloma can be assigned to six substance classes:
- Chemotherapeutic agents: alkylants, antiraclyclines, vincsa alkldoids
- Protease inhibitors
- Immunomodulators
- HDAC inhibitors
- Monoclonal antibodies
- Glucocorticoids

A large number of possible (combination) therapy regimens are available for treatment, so - also due to the high degree of heterogeneity of multiple myeloma - the therapy must be individually tailored to the patient, taking into account current guidelines and directives.

Bortezomib therapy protocols improve prognosis in (6;14) patients with plasma cell myeloma
With therapy protocols containing bortezomib the very unfavourable prognosis for patients with (6;14) could be improved (Avet-Luisseau et al. 2010, Ching et al. 2014, Merz et al. 2018). Patients with del(17p) also benefited from bortezomib when used before and after autologous stem cell transplantation (Neben et al. 2012, Merz et al. 2018). In the study by Merz et al., however, this effect was limited to patients without subclones, regardless of whether the subclonal aberrations were assigned to the high- or standard risk group.

However, the use of bortezomib in autologous stem cell transplantation did not lead to a prognostic improvement in patients with both (6;14) and del(17p), which could be partially circumvented by autologous double stem cell transplantation and therapy regimens containing bortezomib (Cavo et al. 2013).

Patients with an NRAS mutation, but not patients with a KRAS mutation, responded less well to bortezomib, whereas no influence of the NRAS mutation on response and time to progression was demonstrated during therapy with dexamethasone (Mulligan et al. 2014).

BRAF V600E mutation: Predictor of good treatment response in early-stage multiple myeloma
The detection of a BRAF V600E mutation in early-stage multiple myeloma is associated with a good therapeutic response to alkylants, immunomodulators and protease inhibitors (Rustad et al. 2019). According to the current study situation, however, this does not lead to an improved prognosis (prolongation of PFS or OS). It remains to be seen to what extent a targeted therapy with the BRAF inhibitor vemurafenib will improve the prognosis. In any case, a targeted therapy modality exists.

Preliminary stop of clinical studies on the use of venetoclax in multiple myeloma
Good response rates with the BCL2 inhibitor venetoclax were observed for (11;14) patients in relapse (Kumar et al. 2016; Moreau et al. 2017; Touzeau et al. 2017; Gonsalves et al. 2018; Pawlyn & Davies 2019). However, the inclusion of patients in studies on the use of venetoclax in relapsed/refractory multiple myeloma was stopped by the FDA for the time being because a Phase III study in the venetoclax arm had resulted in an increased number of deaths compared to the control arm (HR = 2.03; FDA press release).

Recommendation
Due to "aspiration artifacts", such as dilution by peripheral blood or focal infiltration, the actual plasma cell infiltration can be underestimated in the cytomorphological and flow cytometric assessment of bone marrow aspirates. According to recommendations of the European Myeloma Network (EMN), an additional bone marrow biopsy should therefore be performed (Caers et al. 2018). If discrepancies arise in the determination of plasma cell infiltration on biopsy and aspirate, the IMWG consensus is that the higher of the two values should be used (Rajkumar et al. 2014). Table 6 gives an overview of which examination methods the EMN recommends at which time points (selection according to Caers et al. 2018).

Table 6: Overview of diagnostic recommendations of the EMN at different examination times taking into account the examination material (after Caers et al. 2018)
Bone marrow

<table>
<thead>
<tr>
<th>Method</th>
<th>Diagnosis</th>
<th>At response</th>
<th>At follow-up</th>
<th>At relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM cytology and biopsy</td>
<td>mandatory</td>
<td>mandatory</td>
<td></td>
<td>mandatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(for patients in complete response)</td>
<td></td>
<td>(for patients with light chain escape, oligosecretory disease)</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>recommended</td>
<td>optional</td>
<td></td>
<td>optional</td>
</tr>
<tr>
<td>Cytogenetics using FISH</td>
<td>mandatory **</td>
<td>Not required</td>
<td>Not required</td>
<td>optional</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Periphery Blood</th>
<th>Date of examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Blood count and blood smear</td>
<td>mandatory</td>
</tr>
<tr>
<td>NGS</td>
<td>optional</td>
</tr>
</tbody>
</table>

* The definition of complete response (CR) includes a cytomorphological criterion (proportion of plasma cells in the bone marrow aspirate < 5%) (Kumar et al. 2016)

** In any case the t(4;14) and del(17p) should be investigated. In addition, it is recommended to detect/exclude the following aberrations: t(14;16), 1q21 gain, del(13q22)

Further plasma cell neoplasms

**MGUS and SMM: Different symptoms but genetic similarities with multiple myeloma**

Patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) do not exhibit the clinical symptoms of patients with multiple myeloma, but there are many similarities in genetic changes. It has been shown for various chromosomal aberrations that they were already present in the asymptomatic preliminary stage, but the frequency of the aberration increased as the disease progressed (Lopez-Carral et al. 2012). For patients with SMM, the incidence of 13q deletions is lower in MGUS (20%) than in multiple myeloma (45 - 58%).

**MGUS**

About 40% of patients with MGUS show a hyperdiploid chromosome set. Rearrangements involving the IGG locus are observed in about 30 - 40% of patients, with t(11;14) (9 - 22%), t(4;14) (2 - 3%) and t(14;16) (1 - 4%) being the most frequent translocations (Chiecchio et al. 2009, Bacher et al. 2010, Lakshman et al. 2018). For the rearrangements t(14;16) and t(14;23), which are associated with an unfavourable prognosis in patients with multiple myeloma, no prognostic relevance could be demonstrated in MGUS patients (Boyd et al. 2012). The incidence of 13q deletions is lower in MGUS (20%) than in multiple myeloma (45 - 58%).

The rate of progression in MGUS is approximately 1% per year, and the factors that promote progression are subject to current research. As observed for the SMM, for example, the aberrations del(17p) and t(4;14) are associated with an increased risk of progression (Merz et al. 2018, Lakshman et al. 2018). An elevated M protein level in the blood (M protein > 1.5 g/dl) was also a factor mediating a risk of progression in the study by Merz et al. (Leukemia 2018).

**Prognosis calculation**

Here you reach the prognosis calculation of the MGUS prognosis score.

**SMM**

For patients with SMM, risk groups were defined in terms of progression to symptomatic myeloma depending on the most common chromosomal changes. For t(4;14) and del(17p), for example, it has been shown that they are associated with an increased risk of progression and that patients become more rapidly in need of treatment (Rajkumar et al. 2013). According to one study, this association also exists for 1q gains (Neben et al. 2013). Multiple trisomies in SMM are also associated with a shorter time to progression to symptomatic myeloma, but the prognostic significance of hyperdiploidy changes over the course of the disease is associated with a more favourable prognosis in patients with multiple myeloma (Neben et al. 2013). The del(13q) and t(11;14) have no significant influence on disease progression (Rajkumar et al. 2013). Accordingly, when diagnosing a SMM for risk classification, FISH analyses are recommended for the detection of 1q gains, the deletions 17p, 13q and 1p and the translocations t(11;14), t(4;14) and t(14;16) (Chiecchio et al. 2014).

Currently, there is no therapeutic indication for SMM. However, there is a controversial discussion in the literature whether SMM patients, especially in the high-risk group, could benefit from an early intervention (Kumar & Rajkumar 2018, Mateos & Gonzalez-Calle 2018, Kumar 2018). A study with 199 high-risk SMM patients (defined by specific M-protein levels, plasma cell fraction in bone marrow and the proportion of residual non-malignant plasma cells) showed that treatment with a lenalidomide and dexamethasone combination therapy resulted in delayed progression and improved survival compared to the observation cohort (Mateos et al. 2013). The treatment regime did not affect the efficiency of further therapies, if necessary due to progress (Kumar & Rajkumar 2018). Further studies are needed to evaluate the clinical benefit of early intervention in high-risk SMM, especially in light of the introduction of SLiM criteria and the advances in multiple myeloma diagnosis (Rajkumar et al. 2014, Kumar 2018). A large number of studies with this objective are currently being planned or conducted (Mateos & Gonzalez-Calle 2018).
References

You can find the corresponding references here: