Diagnosis and monitoring of multiple myeloma patients

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SUMMARY

The diagnosis of multiple myeloma (MM) can be challenging, especially in patients with light-chain or non-secretory disease. The disease should be excluded in patients presenting with unexplained anaemia or renal failure and suspected in patients with signs of back pain combined with other systemic symptoms, such as fatigue and weight loss, or back pain combined with abnormal blood tests. The diagnosis is based on clinical, biological and radiological abnormalities that are resumed in the current article. At diagnosis, additional cytogenetic testing is important to determine the prognosis and guide physicians in their treatment choices. The disease is generally monitored by quantifying the monoclonal proteins in blood or urine. The follow-up of patients can be further tailored to the patients' general status, obtained response and disease characteristics.

INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell (PC) proliferation, often associated with the secretion of a monoclonal immunoglobulin. Previously, treatment was initiated solely on the presence of end-organ damage felt to be related to the underlying malignancy (CRAB criteria: hyper**C**alcemia, **R**enal impairment, **A**naemia, **B**one lesions). In 2014, three biomarkers (annotated as SLiM) were added (i.e. bone marrow plasma cells ≥60%, an involved/uninvolved Serum-free light-chain (sFLC) ratio ≥100, or >1 focal lesion found on magnetic resonance imaging [MRI]) allowing for pre-emptive therapy even in the absence of CRAB.[1]

The clinical presentation of MM is highly variable and often tests the clinical acumen of the physician. It requires a high level of suspicion. The diagnostic work-up of MM entails an elaborate blood and urine analysis, a bone marrow examination and imaging studies.

BLOOD ANALYSIS

MM is most frequently associated with the secretion of an intact monoclonal immunoglobulin, referred to as the M-spike or M-component. A serum protein electrophoresis (SPEP) can raise the suspicion of such an M-spike and further allows its quantification. Immunofixation (IF) is mandatory at diagnosis to confirm the monoclonality of the suspected M-spike and for heavy- and light-chain identification.

Other recommended blood tests include a complete blood count and differential count (evaluation of concomitant cytopaenia or circulating plasma cells), renal and liver function tests, calcium, phosphate, uric acid and C-reactive protein (CRP). Albumin, lactate dehydrogenase (LDH) and beta-2 microglobulin (B2M) are recommended for prognostic purposes (see below). Total IgG, IgA and IgM quantification by nephelometry allows an indirect M-spike quantification and the identification of immunoparesis.

Quantification of sFLCs is indicated at diagnosis in all patients with suspected monoclonal gammopathy. The reimbursement criteria in Belgium are unfortunately not that liberal. We recommend that it should be performed once in all suspected MM patients at diagnosis. An involved/uninvolved sFLC ratio > 100 is a SLiM criterium and can be an indication to start anti-MM therapy.

URINE ANALYSIS

Urine analysis, and especially the 24-hour urine collection have always been highly debated analytical tools in the diagnosis of MM (and especially follow-up). This is related to the fact that the collections are often (1) inconsistently performed (resulting in incomplete sampling); (2) they are laborious and sociably difficult to perform; (3) difficulties are encountered in interpreting results due to fluctuations in renal function and (4) sFLC determination is a more convenient technique.

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TABLE 1. Diagnostic exams to perform in case of clinical suspicion of MM.
Medical history & clinical examination
Complete blood count
Serum calcium and creatinine
LDH, Albumin, Beta-2 microglobulin
Serum protein electrophoresis and immunofixation
Quantitation of immunoglobulins (IgA, IgG, IgM)
Urine protein electrophoresis and immunofixation
24-hour urine collection
sFLC assay (in case of light chain MM or oligosecretory disease)
Whole body, low dose CT or MRI if indicated
Bone marrow aspiration and biopsy with cytogenetics

A French study, focusing on patients with light-chain MM, demonstrated that the sFLC assay is superior to 24-hour urine collection (i) in identifying patients with measurable disease, (ii) following their response to initial therapy and (iii) giving a prognostic indication on patients' response and overall survival (OS).[2] This study included 113 patients with light-chain MM and all patients presented with an abnormal sFLC ratio and measurable disease parameters in serum, while only 64% patients had measurable M-proteins in urine protein electrophoresis. Similar results were found in an analysis of 576 patients with light-chain MM from the UK Myeloma IX and XI trials.[3] The disease burden of 567 patients with light-chain MM could be measured and monitored by UPEP in 80% of the patients. For the remaining patients with unmeasurable disease via urine, 113 patients (97%) had involved sFLC >100mg/l, sufficient to measure response to therapy. A recent study performed at the Mayo Clinic compared results of the sFLC assay to detect a progressive disease in patients with light-chain MM. Patients with progressive disease, defined by an increase in 24-hour proteinuria, had a median absolute increase in the sFLC assay of 74 mg/dL; while 89% of patients had an increase ≥25% and 94% had an absolute increase in the difference between involved and uninvolved sFLCs (dFLC) of more than 10 mg/dL. The authors concluded that serial dFLC assessments can replace serial 24-hour urine protein assessments during myeloma surveillance to monitor for disease progression.[4]

We believe that these 3 studies give convincing arguments to use the sFLC assay in monitoring patients with both oligosecretory and light-chain MM, although the IMWG still recommends 24-hour urine collection.[5] The latter is based on an ECOG study that included 399 MM patients (not restricted to light-chain MM only) reporting that the correlation between sFLC assay and 24-hour protein analysis was insufficient to consider the tests interchangeable.[6] At diagnosis, a 24-hour urine collection still remains the golden standard, and we recommend to perform a reliable 14-hour urine analysis at diagnosis, including urinary densitometry, urinary SPEP and IF. In patients with albuminuria, an underlying glomerulopathy should be excluded.

BONE MARROW EXAM

A bone marrow (BM) aspirate allows for enumeration of plasma cells (PC), confirmation of clonality by flow cytometry and cytogenetical analysis. Although reliable quantification of PC is of clinical importance (≥60 % PC infiltration is biomarker for active MM), aspirates often tend to be haemodiluted and BM involvement is frequently anatomically heterogeneous, often called a pathy disease.[7] A simultaneous trephine biopsy can overcome the former and is therefore recommended.

CYTOGENETICAL ANALYSIS

MM is a clinically heterogeneous entity ranging from an indolent disease with survivals surpassing 10 years to a very aggressive disease with a protracted course. This variability is driven by cytogenetic events and therefore their detection has significant prognostic impact. Many different techniques have been evaluated ranging from conventional karyotyping, comparative genomic hybridisation-array, fluorescence in situ hybridization (FISH), single nucleotide polymorphism (SNP)-based mapping, gene-expression profiling and next generation sequencing (NGS). In daily practice, interphase FISH performed either on purified CD138+ cells, or on immunoglobulin counter-stained cells is adequate. The IMWG recommends FISH testing for gain(1q), del(1p), t(4;14)(p16;q32), t(14;16(q32;q23), del(17p13), and a marker for aneuploidy. However, for routine diagnosis, testing of t(4;14) and del(17p13) is sufficient.[8]

IMAGING

In the past, the detection of lytic bone lesion depended on plain X-rays of the skeleton. Nowadays, this technique has been replaced by whole-body, low-dose CT without contrast as a more sensitive, convenient and faster alternative.[9] A whole

TABLE 2. Standard IMWG uniform response criteria for MM.

Stringent complete response	Complete response as defined below plus normal sFLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry
Complete response	Negative IF on the serum and urine and disappearance of any soft tissue plasmacytoma and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours
Partial response	≥50% reduction of serum M-protein plus reduction in 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hours; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required If serum and urine M-protein are unmeasurable, and sFLC assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50-89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: - Serum M-protein (absolute increase must be ≥0·5 g/dL); - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; - Urine M-protein (absolute increase must be ≥200 mg/24 hours); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved sFLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved sFLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of (a) new lesion(s), ≥50% increase from nadir of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

body PET-CT may be used as an alternative as long as a thin slice CT acquisition protocol is applied, allowing for the detection of small (<5 mm) osteolytic lesions.[10] PET-CT allows for a functional imaging by detecting hypermetabolic lesions and the simultaneous detection of extramedullary disease. MRI is of importance in patients with suspected spinal cord compression. Whole body MRI (or at least axial MRI) should be performed in presumed asymptomatic MM patients, for the detection of focal lesions (more than one focal lesion is a biomarker of active MM).

PROGNOSIS OF MM

MM is a clinicaly heterogeneous disease with a diverse clinical behaviour. Several prognostic systems based on the disease specific characteristics have been developed. In 2005, the ISS was introduced, which incorporated serum albumin and B2M (reflecting tumour cell burden, cellular turnover, renal function and nutritional/performance status).[11] This system was updated (R-ISS) by the IMWG and added high LDH and high-risk cytogenetics as detected by FISH to the former ISS scoring system.[12]

In addition to disease specific features, patient characteristics also have a severe impact on therapy tolerability, disease outcome and survival. Therefore it is recommended to perform a comprehensive assessment, especially in frail and elderly patients. The IMWG frailty index incorporates age,

Charlson comorbidity index, activities of daily living (ADL) and instrumental activities of daily living (iADL) and discriminates fit from intermediate and frail patients.[13] Although prospective randomized trials in this field are lacking, correct assessment of frailty and corresponding therapy adaptations will likely result in better therapy adherence, lower rates of side effects and perhaps better outcomes.

MONITORING

Patients should be evaluated before initiation of each treatment cycle to determine their response to therapy. For MM patients with a measurable M-component, the recommended method for monitoring is the quantification of serum and urinary M-protein. Whether all serum (and especially urine) parameters have to be checked after each cycle, rather than after each 2-3 cycles is left to the discretion of each physician, taking into account disease aggressiveness, organ impairment and various other factors. Patients presenting with oligo-secretory disease should be monitored by the sFLC assay, which is also useful for following light-chain MM. If the SFLC assay is not informative, BM plasmacytosis should be assessed. Truly non-secretory disease, with no measurable M-protein or FLC secretion, can be evaluated by combining functional imaging and BM aspiration.

Table 2 resumes the standard IMWG response criteria.[14] The previously defined stringent complete response will probably be replaced by the minimal residual disease (MRD) status that has a superior prognostic impact. Technologic advances in molecular testing using multiparameter flow cytometry, ASO-PCR, NGS, and imaging techniques such as PET-CT, have enabled the detection of myeloma cells with greater sensitivity and are able to recognize residual myeloma cells up to a 10^{-6} sensitivity. Relapse occurs when a patient, who was in CR, experiences a re-appearance of the MM, while progression refers to patients with an increasing disease burden from a baseline of persistent residual disease. A second assessment for confirmation is mandatory. MM progression can either be assessed via laboratory (increase in an existing monoclonal peak), radiological and/or clinical criteria.

The intervals between follow-up visits depend on the obtained response, risk profile of the disease and patient characteristics. They are longer for patients with low-risk disease that are in complete remission, while a closer follow-up is required for patients with biological progression or a high-risk disease. For frail patients it might be helpful to implicate the family physician. At relapse, imaging studies should be realised when symptoms of bone disease and PET/CT should be considered for high-risk patients.

CONCLUSIONS

MM should be suspected in patients presenting signs of back pain combined with other systemic symptoms such as fatigue and weight loss, or back pain combined with abnormal blood tests. Confirmation of a monoclonal gammopathy and an increased (>10%) BM plasmacytosis are key determinants for the final diagnosis of MM. Monitoring after an active treatment is generally based on serum/urine tests and imaging is required when new symptoms arise.

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