25.3. International Myeloma Working Group guidelines


These guidelines discuss published data that provides evidence for the utility and application of sFLC assays for most plasma cell disorders, including symptomatic MM, nonsecretory MM (NSMM), light chain MM (LCMM), SMM, MGUS, solitary plasmacytoma and AL amyloidosis. Furthermore, the guidelines highlight key recommendations for the use of sFLC assays in screening, prognosis and in the assessment of patient response to treatment. Specific emphasis is placed on distinguishing between proven utility and those potential utilities that remain under investigation.

Screening

sFLC assays are recommended for use in combination with serum protein electrophoresis (SPE) and serum immunofixation electrophoresis (sIFE) to screen for pathological monoclonal plasma cell proliferative disorders although if AL amyloidosis is suspected, a 24-hour urine, immunofixation electrophoresis (uIFE) should also be performed.

Prognosis

It is recommended that baseline sFLC assay results are obtained at diagnosis for all patients with MGUS, SMM or active MM, solitary plasmacytoma and AL amyloidosis. Highly abnormal results have prognostic value in virtually every plasma cell disorder. Notably, in MGUS, SMM and plasmacytoma, a highly abnormal sFLC ratio indicates a substantial risk of progression to systemic disease.

Monitoring and response assessment

sFLC assays are recommended for the quantitative monitoring of patients with oligosecretory plasma cell disorders, including patients with AL amyloidosis, oligosecretory myeloma, and in nearly two-thirds of patients previously classified as having NSMM. Furthermore, in the absence
of urinary evaluations or FLC measurements, light chain escape can be missed and so these tests should be performed periodically. Baseline results of sFLC testing are required prior to initiating new chemotherapy regimens for all patients with MM to determine if a stringent complete response has been attained after a complete response has been achieved. Despite limited published data validating the use of sFLC assays in patients with light chain deposition disease, it is stated that the personal experience of the guideline authors confirms their utility in these cases.

25.3.2. Guidelines for monoclonal gammopathy of undetermined significance and smouldering multiple myeloma (2010)

For patients with MGUS, the size of the monoclonal protein, type of monoclonal protein, sFLC ratio, as well as the proportion of aberrant plasma cells within the bone marrow are helpful in identifying patients who are at increased risk of progression [2][3][4][5][6]. These International Myeloma Working Group (IMWG) guidelines [7] recommend that patients with MGUS should be risk stratified at diagnosis, to optimise counselling and follow-up, using a model incorporating the following risk factors: 1) serum monoclonal immunoglobulin ≥15 g/L; 2) serum monoclonal immunoglobulin type (IgA or IgM); and 3) abnormal $\kappa/\lambda$ sFLC ratio (Table 25.3 and Chapter 13). For patients with low-risk MGUS, a baseline bone marrow examination or skeletal radiography is not routinely indicated. For patients with intermediate- and high-risk MGUS a bone marrow aspirate and biopsy should be carried out at baseline to rule out any underlying plasma cell malignancy [7].
<table>
<thead>
<tr>
<th>MGUS risk group</th>
<th>Criteria</th>
<th>Absolute risk* (%)</th>
<th>Recommended follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No risk factors present</td>
<td>2</td>
<td>6 months initially, and if stable, follow up every 2 - 3 years or when symptoms suggest a plasma cell malignancy</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>Any one risk factor present</td>
<td>10</td>
<td>6 months initially, then annually and upon any change in the patient's clinical condition</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>Any two risk factors present</td>
<td>18</td>
<td>6 months initially, then annually and upon any change in the patient's clinical condition</td>
</tr>
<tr>
<td>High</td>
<td>All three risk factors present</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

*of progression at 20 years accounting for death as a competing risk. Risk factors are defined as serum monoclonal immunoglobulin ≥15 g/L, serum monoclonal immunoglobulin type (IgA or IgM) and an abnormal sFLC κ/λ ratio.

Table 25.3. Summary of MGUS risk groups and recommended follow-up.

For patients with SMM, the guidelines recommend SPE plus electrophoresis of a 24-hour urine, to confirm the diagnosis and full blood cell count plus serum calcium and creatinine measurements to rule out MM, at baseline and after 2 - 3 months. Baseline sFLC measurements are required for risk stratification and a baseline bone marrow biopsy and skeletal survey are mandatory. If the results are stable, the studies should be repeated every 4 - 6 months for the first year, and then, if remaining stable, the follow-up period can be lengthened to 6 - 12 months.

25.3.3. Guidelines for standard investigative work-up of patients with suspected multiple myeloma (2011)

sFLC analysis is recommended as part of the standard investigative work-up in all newly diagnosed patients with plasma cell dyscrasias. It was noted that sFLC testing is particularly important in patients with NSMM and LCMM, as well as in other patients with oligosecretory myeloma. Measurement of urine FLC levels is not recommended.
25.3.4. Guidelines for risk stratification in multiple myeloma (2011)

Evaluation of prognostic factors and risk stratification in newly-diagnosed patients is important to define treatment strategies, compare outcome of therapeutic trials and predict survival from diagnosis. The 2011 IMWG guidelines for risk stratification[9] state that the International Staging System (ISS) [10], incorporating serum albumin and β2-microglobulin (β2M), is applicable as a prognostic system in the majority of settings (Section 20.1).

The guidelines state that other factors may play significant roles in risk stratification, including extramedullary or plasmablastic disease, plasma cell leukaemia, renal failure, lactate dehydrogenase (LDH), IgA, high sFLCs and an abnormal κ/λ sFLC ratio.

Earlier staging systems included concentrations of monoclonal immunoglobulins. It has now been realised that these have little relevance to MM outcome. For IgG MM this may be due to variable recycling by FcRn receptors (Chapter 3). By contrast, elevated sFLC concentrations and abnormal κ/λ sFLC ratios do relate to disease stage and outcome (Chapter 20). This may be due to their more consistent clearance, capacity to cause renal damage (Chapter 26), and their association with IgH translocations [11].

25.3.5. Consensus criteria for response and minimal residual disease assessment in multiple myeloma (2016)

Consensus criteria for response and minimal residual disease (MRD) were published in 2016 [12], a decade after IMWG recommendations for the uniform reporting of clinical trials were first published [13][14][15]. These new criteria, summarised in Table 25.4, define new minimal residual disease response categories (for patients who have achieved a complete response), that are based on flow cytometry, gene sequencing or imaging techniques. It is proposed that all future clinical trials in MM should follow these guidelines when reporting results.

Required baseline and follow-up tests for response assessment using IMWG consensus criteria

The κ/λ sFLC ratio is required for all patients to define a stringent CR. It should also be performed for all patients at suspected CR as well as at suspected clinical or biochemical progression. In addition, normalisation of sFLCs should also be performed at every time point (every cycle) for patients in whom the only measurable disease is by sFLC levels (Table 25.4).

The guidelines also discuss a potential role for Hevylite in the definition of MRD. Once patients are classified as IMWG MRD negative (by cell-based assays and imaging), normalisation of the Hevylite ratio may provide further evidence of tumour eradication and immune system recovery. Further
study of Hevylite as a marker of MRD is encouraged.

<table>
<thead>
<tr>
<th>Response subcategory</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained MRD-negative</strong>*</td>
<td>• MRD negativity in the marrow by next-generation sequencing (NGS) or next-generation flow (NGF), or both, and MRD negativity by imaging, as defined below, confirmed minimum of 1 year apart</td>
</tr>
<tr>
<td><strong>Flow MRD-negative</strong>**</td>
<td>• Absence of phenotypically aberrant plasma cells by NGF on bone marrow aspirates with a minimum sensitivity of 1 in $10^5$ nucleated cells</td>
</tr>
<tr>
<td><strong>Sequencing MRD-negative</strong>*</td>
<td>• Absence of clonal plasma cells by NGS on bone marrow aspirate with a minimum sensitivity of 1 in $10^5$ nucleated cells</td>
</tr>
<tr>
<td><strong>Imaging-positive MRD-negative</strong></td>
<td>• MRD negativity as defined by NGF or NGS, and • Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool standardised uptake values or decrease to less than that of surrounding normal tissue</td>
</tr>
<tr>
<td><strong>Stringent complete response (sCR)</strong></td>
<td>CR as defined below, and • Normal FLC ratio, and • Absence of clonal plasma cells by immunohistochemistry</td>
</tr>
<tr>
<td><strong>Complete response (CR)</strong></td>
<td>• Negative IFE of serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • &lt;5% plasma cells in bone marrow aspirates • *In patients in whom the only measurable disease is by sFLC levels, CR is defined as a normal FLC ratio (0.26-1.65) in addition to the CR criteria listed above</td>
</tr>
<tr>
<td><strong>Very good partial response (VGPR)</strong></td>
<td>• Serum and urine M-protein detectable by IFE but not on electrophoresis, or • ≥90% reduction in serum M-protein plus urine M-protein &lt;100 mg per 24 hours • *In patients in whom the only measurable disease is by sFLC levels, VGPR is defined as a &gt;90% decrease in the difference between involved and uninvolved sFLC levels</td>
</tr>
</tbody>
</table>
| Partial response (PR) | ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hours
| In patients in whom the only measurable disease is by sFLC levels, PR is defined as a ≥50% decrease in the difference between involved and uninvolved sFLC levels
| If serum and urine M-protein are unmeasurable, and sFLCs are also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30%
| In addition to the above criteria, if present at baseline, ≥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-h urine M-protein by 50-89%, and
| If present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas |
| Stable disease (SD) | Not meeting criteria for CR, VGPR, PR or progressive disease |
| Progressive disease (PD) | Any one or more of the following:
| Increase of 25% from lowest confirmed response value in any one or more of the following:
| ○ Serum M-protein (absolute increase must be ≥5 g/L) and/or
| ○ Urine M-protein (absolute increase must be ≥200 mg/24 hours) and/or
| ○ In patients in whom the only measurable disease is by sFLC levels, the difference between involved and uninvolved sFLC levels (absolute increase must be >100 mg/L)
| ○ If serum and urine M-protein are unmeasurable, and sFLCs are also unmeasurable, bone marrow plasma cell percentage (absolute % must be ≥10%)
| Appearance of new lesions, ≥50% increase from nadir in SPD of >1 lesion, or a ≥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 |

*Subsequent evaluations can be used to further specify the duration of negativity (e.g. MRD-negative at 5 years)
**Using EuroFlow standard operation procedure for MRD detection in MM, or validated equivalent method
***Presence of a clone defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform or validated equivalent method
Note that all response categories require two consecutive assessments made at any time before the institution of any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-protein increases of ≥10 g/L are sufficient to define relapse if baseline M-protein is ≥50 g/L.

Table 25.4. IMWG criteria for response and MRD assessment in MM [12].

In patients with measurable disease by SPE or UPE (defined as serum monoclonal protein ≥10 g/L; urine monoclonal protein ≥200 mg/24 hours), or both, will be assessed for response based only on these two tests, and not by FLC assays. In these patients, FLC assays are only required for assessment of stringent complete response.

In patients in whom the only measurable disease is by sFLC levels (defined as involved FLC ≥100 mg/L, provided that the FLC ratio is abnormal), the definition of partial or very good partial sFLC response requires subtraction of the tumour ("involved") FLC from the non-tumour ("uninvolved") FLC. This difference calculation provides an interpretable result even when the non-tumour FLC is below the detection limit or fluctuating widely (thereby making the sFLC ratio unreliable). It is also helpful when interpreting high concentrations of the alternate FLC, as observed in patients with impaired renal function (Chapter 27).

25.3.6. Recommendations for global myeloma care (2013)

The IMWG recommendations for global myeloma care [16] outline the minimal requirements for the diagnosis and monitoring of patients with MM. The aim of this publication was to provide relevant information and recommendations for clinicians worldwide, taking into consideration the substantial differences in healthcare systems.

At diagnosis, all of the following tests should be performed: SPE, UPE of a 24-hour urine specimen, serum and urine IFE and sFLC analysis. It is also recommended that sFLC measurements are used to monitor disease course, particularly in patients with oligosecretory or nonsecretory MM.

25.3.7. Recommendations for the diagnosis and management of myeloma-related renal impairment (2016)
For the diagnosis of renal impairment in patients with MM, the IMWG recommend that all patients (at diagnosis and at disease assessment) have serum creatinine and electrolytes measurements, as well as sFLC analysis and 24-hour urine electrophoresis. The IMWG recommendations also discuss the use of quantitative sFLC values in the evaluation of renal impairment in MM: if a patient has high sFLCs (defined as a concentration above a specified range of values [500 - 1500 mg/L]) and proteinuria (in which light chains predominate), then a diagnosis of cast nephropathy is likely and a renal biopsy is probably not necessary (but may be helpful in selective cases). If a patient has relatively low sFLCs (<500 mg/L) and non-selective proteinuria/significant albuminuria, then an alternative diagnosis (e.g. MIDD or AL amyloidosis) should be considered and a renal biopsy is often necessary.

References

6. Perez-Persona E, Vidriales MB, Mateo G, Garcia-Sanz R, Mateos MV, de Coca AG et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain


