Multiple myeloma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence
The incidence of multiple myeloma (MM) in Europe is 6.0/100 000/year with a median age at diagnosis of between 63 and 70 years; the mortality is 4.1/100 000/year.

diagnosis
Diagnosis should be based on the following tests:

- Detection and evaluation of the monoclonal (M-) component.
- Serum and urine protein electrophoresis (concentrate of 24-h urine).
- Quantification of IgG, IgA and IgM immunoglobulins.
- Characterization of the heavy and light chains by immunofixation. Serum free light chain measurement for identifying and monitoring non secretory MM.
- Evaluation of bone marrow plasma cell infiltration. Bone marrow aspiration and biopsy are the standard option to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells.
- Evaluation of lytic bone lesions.
- Full skeleton X-ray survey is recommended. Optional magnetic resonance imaging (MRI) provides greater details and is recommended if a spinal cord compression is suspected.
- Biological assessments to differentiate symptomatic and asymptomatic MM: hemoglobin (and full blood cell count), serum creatinine and calcium level (CRAB classification).

These tests allow the differential diagnosis between MM, smoldering (or indolent) MM and monoclonal gammopathy of undetermined significance (MGUS).

staging and risk assessment
The most commonly used staging system is still the Durie–Salmon classification (Table 1).

A number of biological parameters are of prognostic importance (β₂-microglobulin, C-reactive protein, LDH, serum albumin). The level of β₂-microglobulin is most commonly used. Combining it with serum albumin has lead to a new International Staging System (ISS) (Table 2).

Cytogenetics is a major prognostic factor and should be obtained either by conventional karyotyping or FISH analysis. The most relevant abnormalities are del(13), t(4;14) and del(17p), which are associated with a poorer outcome.

treatment plan
stage I or asymptomatic myeloma
Immediate treatment is not recommended for patients with indolent myeloma.

advanced stage or symptomatic myeloma (CRAB) (II or III)

elderly patients. Until now, oral combination of melphalan plus prednisone (9 mg/m²/day for 4 days) and prednisone (30 mg/ m²/day for 4 days) has been the standard of treatment for patients ineligible for high-dose chemotherapy with stem-cell support [I, A]. Cycles are repeated every 4–6 weeks until a stable response is achieved. Multiagent chemotherapy has not been proved superior and may even be inferior in elderly patients [I, A].

However, two recent randomized studies have shown that the combination of melphalan–prednisone with thalidomide (100 mg/day) is superior to melphalan–prednisone. Other novel agents (bortezomib, lenalidomide) are currently being tested in combination with melphalan–prednisone in patients >65 years of age.

In patients who have a stable response to initial treatment (plateau phase) chemotherapy can be stopped safely.

Younger patients (<65 years). For patients in good clinical condition high-dose therapy with autologous stem-cell transplantation (ASCT) is the standard treatment [II, B].
Melphalan 200 mg/m² i.v. is the preparative regimen before autologous transplantation [II, B]. Peripheral blood progenitor cells should be used as the source of stem cells, rather than bone marrow [III, B].

Double ASCT: three randomized studies show superiority of double versus single ASCT; however, only one shows a benefit in overall survival. The Italian study (IFM 94) confirms that double ASCT does not benefit patients in complete remission after one ASCT.

Attempts to increase the complete remission rate before autologous transplantation are ongoing. Currently, the induction therapy should be dexamethasone based in order to avoid stem-cell damage induced by alkylating agents. The classical VAD regimen (vincristine, Adriamycin and high-dose dexamethasone) is being challenged by combinations of dexamethasone with thalidomide or with other novel agents (bortezomib, lenalidomide).

**consolidation**

There is no convincing evidence that post-transplantation therapy with interferon is useful but based on a recently updated Australian study, thalidomide maintenance increases the complete remission rate and prolongs progression-free survival (PFS) and overall.

Although encouraging data with tandem auto/reduced intensity conditioning allo transplant have recently been published, this strategy should not be proposed for standard-risk patients as first-line treatment due to transplant-related mortality of 10–15% and the risk of chronic GVHD; in high-risk patients upfront allogeneic transplantation should only be performed within clinical trials.

Long-term administration of bisphosphonates (oral or i.v.) reduces the incidence of skeletal events and should be proposed for patients with stage III or relapsed disease receiving conventional dose chemotherapy [II, A].

**treatment of relapsed/refractory myeloma**

Regimens similar to those used initially can induce a second remission.

VAD is no longer considered the standard option for patients in relapse.

Thalidomide is mostly used in combination with dexamethasone and/or chemotherapy (initial dose 100–200 mg/day) and results in an increased risk of deep vein thrombosis; therefore, at least in patients with increased risk (high tumor burden, history of thrombosis) anticoagulation prophylaxis should be administered.

Bortezomib is used either alone or in combination with dexamethasone or with chemotherapy. A recently completed randomized trial shows that bortezomib in combination with pegylated liposomal doxorubicin is superior to bortezomib alone.

Lenalidomide has just been approved in Europe for the treatment of relapsed MM (in combination with dexamethasone).

**response evaluation**

Assessment of response is based on serum and urine electrophoresis.

- In patients with no M-component in serum and urine, complete remission assessment requires bone marrow aspiration (<5% plasma cells) and immunofixation. Evaluation of free light chains and/or their ratio may be helpful.
- Very good partial remission is now accepted as a relevant response level and is defined by disappearance of the M-component (or >90% reduction of the serum M-component) but with positive immunofixation.
- Partial remission is defined by ≥50% reduction of M-gradient in serum and ≥90% reduction in 24-h urine.

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**Table 1.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage I: all of the criteria below</th>
<th>Stage II: one or more of the criteria below</th>
<th>Stage III: one or more of the criteria below</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>&gt;10 g/dl</td>
<td>8.5–10.0 g/dl</td>
<td>&lt;8.5 g/l</td>
</tr>
<tr>
<td>Calcium</td>
<td>&lt; 3.0 mmol/l</td>
<td>&lt;3.0 mmol/l</td>
<td>&gt;3.0 mmol/l</td>
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<tr>
<td>M-protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>&lt;30 g/l</td>
<td>30–50 g/l</td>
<td>&gt;50 g/l</td>
</tr>
<tr>
<td>IgG</td>
<td>&lt;50 g/l</td>
<td>50–70 g/l</td>
<td>&gt;70 g/l</td>
</tr>
<tr>
<td>Urine light chain</td>
<td>&lt;4 g/24 h</td>
<td>4–12 g/24 h</td>
<td>&gt;12 g/24 h</td>
</tr>
<tr>
<td>Bone X-ray subclassification:</td>
<td>Normal</td>
<td></td>
<td>Three lytic bone lesions</td>
</tr>
<tr>
<td></td>
<td>Stage A</td>
<td>Serum creatinine &lt;177 µmol/l</td>
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</tr>
<tr>
<td></td>
<td>Stage B</td>
<td>Serum creatinine ≥177 µmol/l</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.**

| IPI Group I | β₂M <3.5 mg/l and serum albumin >3.5 g/dl |
| IPI Group II| β₂M <3.5 mg/l and serum albumin >3.5 g/dl  |
|            | or β₂M 3.5–5.5 mg/l                     |
| IPI Group III| β₂M >5.5 mg/l                          |

β₂M, β₂-microglobulin.
follow-up

Full blood count, serum and urine electrophoresis or/and free light chain determination in serum or urine, creatinine, calcium, and β2-microglobulin should be carried out every 3–6 months. In case of bone pain, skeletal X-ray or MRI should be performed to detect new bone lesions.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

literature