

## Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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### incidence

The incidence of multiple myeloma (MM) in Europe is 4.5–6.0/100 000/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 by 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 and oligo-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 spinal cord compression is suspected.

Biological assessments to differentiate symptomatic and asymptomatic MM: haemoglobin (and full blood cell count), serum creatinine and calcium level (CRAB classification).

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

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### staging and risk assessment

Previously, the most commonly used staging system has been the Durie–Salmon classification (Table 1).

A number of biological parameters are of prognostic importance ( $\beta$ 2-microglobulin, C-reactive protein, lactate dehydrogenase and serum albumin). The level of  $\beta$ 2-microglobulin is used most commonly. Combining it with serum albumin has led to a new International Staging System (ISS) which is a more convenient and reproducible classification (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(13q) (karyotype), t(4;14), t(14;16) and del(17p) (FISH), which are associated with a poorer outcome.

### treatment

#### 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.* Oral combination of melphalan and prednisone has been the standard of treatment for patients ineligible for high-dose chemotherapy with stem-cell support, including elderly patients but should now be replaced by combinations with novel agents. Three randomized studies have shown that the combination of melphalan–prednisone with thalidomide (100 mg/day) is superior to melphalan–prednisone [I, A].

Bortezomib in combination with melphalan–prednisone also achieved significantly higher survival rates and a complete remission rate comparable to that achieved with high-dose therapy plus stem-cell transplantation [I, A]. Melphalan–prednisone plus either thalidomide or bortezomib are the new standards in Europe. Lenalidomide combined with low-dose dexamethasone also yields improved response and overall survival rates, and is well tolerated even in patients >65 years of age. The impact of this combination compared with melphalan-containing regimens will be clarified by ongoing trials. *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].

**Table 1.** Durie–Salmon classification of MM

Parameter	Stage I: all of the criteria below	Stage II: one or more of the criteria below	Stage III: one or more of the criteria below
Haemoglobin (g/dl)	>10	8.5–10.0	<8.5
Calcium (mmol/l)	<3.0	<3.01	>3.0
M-protein (g/l)			
IgA	<30	30–50	>50
IgG	<50	50–70	>70
Urine light chain (g/24 h)	<4	4–12	>12
Bone X-ray	Normal	–	Three lytic bone lesions
Subclassification:	Stage A Stage B	Serum creatinine <177 µmol/l Serum creatinine ≥177 µmol/l	

**Table 2.** International staging system

IPI Group I	$\beta_2$ M <3.5 mg/l and serum albumin >3.5 g/dl
IPI Group II	$\beta_2$ M <3.5 mg/l and serum albumin >3.5 g/dl or $\beta_2$ M 3.5–5.5 mg/l
IPI Group III	$\beta_2$ M >5.5 mg/l

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. In randomized studies, combinations of novel agents (thalidomide or bortezomib) plus dexamethasone are superior to the classical VAD regimen (vincristine, adriamycin and high-dose dexamethasone). Triple combinations might be even more effective.

Melphalan 200 mg/m<sup>2</sup> 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, the French (IFM 94) and Italian study suggests that double ASCT does not benefit patients in complete remission after one ASCT. The impact of double ASCT in the era of novel therapies is unclear. 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].

### consolidation

There is no convincing evidence that post-transplantation therapy with interferon is useful, but based on three randomized studies, thalidomide maintenance increases the complete remission rate and prolongs progression-free survival and overall survival. However, the optimal duration of treatment and the respective impact of short consolidation

versus prolonged maintenance is not yet known. The role of other novel agents in this setting and of novel agents given both before and after transplantation is currently under evaluation.

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

### treatment of relapsed/refractory myeloma

Regimens identical to those used initially can induce a second remission, when relapse occurs off therapy. VAD is no longer considered the standard option for patients in relapse.

Thalidomide is used mostly 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 tumour burden, history of thrombosis), anticoagulation prophylaxis should be administered.

Bortezomib is used either alone or in combination with dexamethasone or with chemotherapy. Lenalidomide (in combination with dexamethasone) has been shown to be superior to dexamethasone alone. The use of novel agents at relapse has already dramatically improved overall survival.

### 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 especially in oligo-secretory myeloma.

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-component in serum and >90% reduction in 24-h urine. There is a statistical relationship between complete remission or at least very good partial remission achievement and progression-free survival or overall survival.

## follow-up

Full blood count, serum and urine electrophoresis or/and serum-free light-chain determination, creatinine and calcium should be carried out every 3–4 months (out of a clinical trial). In the 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.

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