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

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incidence and epidemiology

Multiple myeloma (MM) accounts for 1% of all cancers and ~10% of all haematological malignancies. The incidence in Europe is 4.5–6.0/100 000/year with a median age at diagnosis of between 65 and 70 years; the mortality is 4.1/100 000/year. Almost all patients with MM evolve from an asymptomatic pre-malignant stage termed monoclonal gammopathy of undetermined significance (MGUS). MGUS progresses to MM at a rate of 1% per year. In some patients, an intermediate asymptomatic but more advanced pre-malignant stage termed smouldering (or indolent) multiple myeloma (SMM) can be recognised. SMM progresses to myeloma at a rate of 10% per year over the first 5 years following diagnosis, 3% per year over the following 5 years and 1.5% per year thereafter [1].

diagnosis

Diagnosis of MM should be based on the following tests: [1]

- Detection and evaluation of the monoclonal (M-) component by serum and/or urine protein electrophoresis (concentrate of 24 h urine collection); nephelometric quantification of IgG, IgA and IgM immunoglobulins; characterisation of the heavy and light chains by immunofixation; and serum-free light-chain (FLC) measurement;
- Evaluation of bone marrow (BM) plasma cell infiltration: BM aspiration and/or biopsies are the standard options to evaluate the number and characteristics. Moreover, the BM sample should be used for cytogenetic/fluorescence *in situ* hybridization (FISH) studies and also has the potential for immunophenotypic and molecular investigations;
- Evaluation of lytic bone lesions: a radiological skeletal bone survey, including spine, pelvis, skull, humeri and femurs is necessary. A magnetic resonance imaging (MRI) or computed tomography (CT) scan may be needed to evaluate symptomatic bony sites, even if the skeletal survey is negative and the patient has symptoms suggesting bone lesions. Moreover, MRI provides greater detail and is recommended whenever spinal cord compression is suspected. Fluorodeoxyglucose positron emission tomography is currently under evaluation but should not be systematically used;
- Complete blood cell count, with differential serum creatinine and calcium level.

These tests can allow for the differential diagnosis between symptomatic MM, SMM and MGUS (Table 1).

The diagnosis of symptomatic MM requires:

- ≥10% clonal plasma cells on BM examination or a biopsy proven plasmacytoma; and
- evidence of end-organ damage, the so-called CRAB criteria (hypercalcaemia, renal insufficiency, anaemia or bone lesions) that is felt to be related to the underlying plasma cell disorder (Table 1).

staging and risk assessment

The course of MM is highly variable, and the clinical behaviour is remarkably heterogeneous. Many studies have identified prognostic factors capable of predicting this heterogeneity in survival: serum β2-microglobulin, albumin, C-reactive protein and lactate dehydrogenase.

The International Staging System (ISS), a powerful and reproducible three-stage classification (Table 2), relies on the combination of serum levels of β2-microglobulin and of albumin. ISS3 is associated with the poorest outcome [2].

Cytogenetics, evaluated by FISH, is a major prognostic factor. Two recurrent genetic abnormalities, t(4;14) and deletion(17p), are mostly associated with a poorer outcome. Chromosome 1 abnormalities and t(14;16) are also adverse prognostic factors.

It has recently been demonstrated that combining both t(4;14) and del(17p), along with the ISS stage, could

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Table 1. Diagnostic criteria for plasma cell disorders

Disorder	Disease definition
Monoclonal gammopathy of undetermined significance (MGUS)	All three criteria must be met: - Serum monoclonal protein <3 g/dl - Clonal BM plasma cells <10%, and - Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Smouldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Both criteria must be met: - Serum monoclonal protein (IgG or IgA) ≥3 g/dl and/or clonal BM plasma cells ≥10%, and - Absence of end-organ damage such as lytic bone lesions, anaemia, hypercalcaemia or renal failure that can be attributed to a plasma cell proliferative disorder
Multiple myeloma	All criteria must be met: - Clonal BM plasma cells ≥10% or biopsy proven plasmacytoma, and - Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically Hypercalcaemia: serum calcium >11.5 mg/dl or Renal insufficiency: serum creatinine >1.73 μmol/l (or >2 mg/dl) or estimated creatinine clearance <40 ml/min Anaemia: normochromic, normocytic with a haemoglobin value of ≥2 g/dl below the lower limit of normal or a haemoglobin value <10 g/dl Bone lesions: lytic lesions, severe osteopenia or pathologic fractures

Table 2. International staging system.

Stage	Criteria
I	Serum β2M <3.5 mg/l and serum albumin ≥3.5 g/dl
II	Not stage I or III[a]
III	Serum β2M ≥5.5 mg/l

[a]There are two possibilities for stage II: serum β2 microglobulin <3.5 mg/l, but serum albumin <3.5 g/dl, and Serum β2 microglobulin 3.5–5.5 mg/l irrespective of the serum albumin.

Greipp PR, San Miguel J, Durie BGM et al. International Staging System for Multiple Myeloma. J Clin Oncol 2005; 23: 3412–3420. Reprinted with permission. @2005 American Society of Clinical Oncology. All rights reserved.

significantly improve the prognostic assessment in terms of progression-free survival (PFS) and overall survival (OS) [3].

Gene-expression profiling may segregate patients with standard or high-risk disease, but this is not yet established in routine practice.

front-line treatment

asymptomatic myeloma

Immediate treatment is not recommended at the present time for patients with indolent myeloma.

symptomatic myeloma (Figure 1)

Treatment should be initiated in all patients with active myeloma fulfilling the CRAB criteria, (hypercalcaemia >11.0 mg/dl), creatinine >2.0 mg/ml, anaemia (Hb <10 g/dl), active bone lesions), and in those symptomatic due to the underlying disease.

elderly patients (non-transplant setting). Oral combinations of melphalan and prednisone (MP) plus novel agents are considered as standards of care in Europe.

The two following options are recommended based on data from randomised phase III trials [I, A]: melphalan/prednisone/thalidomide (MPT) [4], or bortezomib/melphalan/prednisone (VMP) [5]; both MPT and VMP are approved in this setting by the European Medicines Agency (EMA). Bendamustine plus prednisone is another regimen that is also approved by the EMA in patients who have clinical neuropathy at time of diagnosis precluding the use of thalidomide according to the MPT regimen or bortezomib according to the VMP regimen [6].

Melphalan/prednisone/lenalidomide (MPR) has been evaluated in a prospective randomised study versus MP, but was not superior to the dual combination with a fixed number of cycles [7]. This triplet combination is not approved and cannot be considered as a standard of care.

Cyclophosphamide/thalidomide/dexamethasone (CTD) has also been compared with MP and is superior in terms of response rates, but does not induce a clear survival advantage over MP [8].

Lenalidomide combined with low-dose dexamethasone, widely used in US centres, also yields important response and OS rates [9] but is not approved in Europe. This regimen is currently being compared with MPT in a large randomised phase III trial.

younger patients (<65 years or fit patients in good clinical condition). For patients in good clinical condition (e.g. fit patients), induction followed by high-dose therapy with autologous stem cell transplantation (ASCT) is the standard treatment [II, B] [10, 11]. Response rates to induction therapy have been significantly increased by the use of novel agent-based combinations. Bortezomib-dexamethasone, which is superior to the classical VAD regimen (vincristine, adriamycin and high-dose dexamethasone) [II, B] [12], has become the backbone of induction therapy before ASCT. The addition of a third agent to bortezomib-dexamethasone, e.g. thalidomide (VTD), doxorubicin (DVD or PAD), lenalidomide (RVD) or cyclophosphamide (VCD), has shown higher response rates in phase II trials [13]. Three prospective studies have already shown that VTD is superior to TD or bortezomib-dexamethasone [14–16]. No data are available to assess the

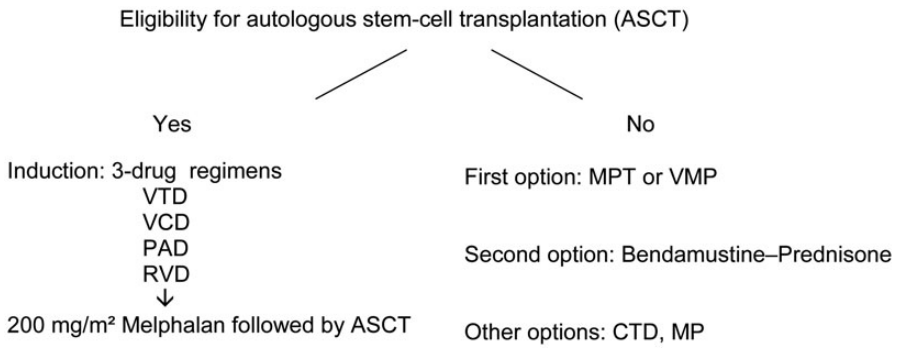

Figure 1. Front-line treatment of symptomatic multiple myeloma outside clinical trials. MPT, melphalan, prednisone, thalidomide; VMP, bortezomib, melphalan, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; MP, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; PAD, bortezomib, doxorubicin, dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone.

superiority of one combination, VTD, RVD, VCD, PAD etc., over another. Based on response rates, depth of response and PFS as surrogate markers for outcome, three-drug combinations including at least bortezomib and dexamethasone are currently the standard of care before ASCT. Three to four courses are recommended before proceeding to stem cell collection.

Melphalan (200 mg/m^2 i.v.) is the standard preparative regimen before ASCT [II, B] [17]. Peripheral blood progenitor cells are the preferred source of stem cells, rather than BM [III, B].

Tandem ASCT has been evaluated before the era of novel agents. The benefit of tandem ASCT was observed in patients that were not reaching very good partial response after the first ASCT [18]. In a recent study from the Netherlands and Germany (Hovon 65-GMMG HD4 trial), in the context of bortezomib induction and maintenance treatment, OS was better in the GMMG group, which carried out tandem ASCT in contrast to HOVON (single ASCT) [19]. Nevertheless, the trial was not powered to compare single versus double high-dose melphalan. Ongoing trials running both in Europe and US comparing prospectively single versus tandem ASCT in the era of novel agents will solve this important issue.

Allogeneic stem cell transplantation should only be carried out in the context of a clinical trial and only in patients with good response before transplant.

consolidation

Thus far, in the era of novel agent-based induction therapy, there is still not enough evidence that consolidation therapy should be systematically applied. The impact of consolidation will be clarified by ongoing trials.

maintenance

In elderly patients following induction, three randomised trials have explored the benefit of maintenance therapy in terms of OS using either immunomodulatory drugs (IMiDs) or bortezomib: MP versus MPR versus MPR-R [7], bortezomib-melphalan-prednisone-thalidomide / bortezomib-thalidomide versus VMP [20], VMP versus VTP followed by either bortezomib-prednisone (VP) or VP maintenance [21]. Due to the trial design, the benefit in OS is not well established. These drugs are not approved by the EMA. Therefore, systematic maintenance therapy is also not recommended in elderly patients.

In young patients following ASCT, phase III randomised trials have demonstrated that maintenance therapy with IMiDs, either thalidomide or lenalidomide, prolongs PFS [I, A] [22, 23], but the OS benefit is still unclear. Bortezomib maintenance is also under evaluation [19]. These three agents are not approved in this setting; therefore, systematic maintenance therapy is not recommended.

response evaluation

The definition of response established by the International Myeloma Working Group in 2006 has recently been modified (Table 3) [24]. The quality and the depth of response have been improved over the last 5 years in the context of novel agent-based therapies allowing for introduction of novel response grades, namely stringent complete response (sCR), immunophenotypic CR and molecular CR to the definition of conventional CR.

There is a statistical relationship between CR achievement and PFS or OS survival.

follow-up

Full blood count, serum and urine electrophoresis and/or serum-FLC determination, creatinine and calcium should be carried out every 2–3 months (outside the context of a clinical trial) [1].

In the case of bone pain, skeletal X-ray, MRI or CT scan should be carried out to detect new bone lesions [1].

treatment of relapsed and refractory disease

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval since the last therapy. The EMA has approved lenalidomide in combination with dexamethasone [25–26] and bortezomib either alone as single agent [27] or in combination with pegylated doxorubicin [28]. Nevertheless, bortezomib is mostly used in combination with dexamethasone in the relapse setting.

Table 3. Response criteria.

Response subcategory	Response criteria
Molecular CR	CR plus negative ASO-PCR, sensitivity 10^{-5}
Immunophenotypic CR	Stringent CR plus Absence of phenotypically aberrant PCs (clonal) in BM with a minimum of 1 million total BM cells analysed by multi-parametric flow cytometry (with >4 colours)
Stringent CR (sCR)	CR as defined below plus Normal FLC ratio and Absence of clonal PCs by immunohistochemistry or 2- to 4-colour flow cytometry
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% PCs in BM
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in PCs is required in place of M-protein, provided baseline BM PC percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required

PCs, plasma cells; BM, bone marrow; CR, complete response; VGPR, very good partial response; PR, partial response; ASO-PCR, allele-specific polymerase chain reaction; FLC, free light chain.

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Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

Thalidomide and bendamustine are effective drugs, often used, but not approved [29]. Triplet combinations have proved effective in phase II trials, but only one single randomised trial has shown the superiority of VTD over TD for PFS in patients relapsing following ASCT [30].

In young patients, a second ASCT may be considered, provided the patient responded well to the previous ASCT and had a PFS of more than 24 months [31]. In the relapse setting, allogeneic SCT should only be carried out in the context of a clinical trial.

When possible, patients should be offered participation in clinical trials. Pomalidomide [29], the third-in-class IMiD, and carfilzomib [29], the second-in-class proteasome inhibitor, both approved in US, are not yet available in Europe outside clinical trials. Other drugs or classes of drugs such as histone-deacetylase inhibitors or monoclonal antibodies are currently under development [29].

personalised medicine

In 2013, no prognostic factor or staging system, including ISS cytogenetics or gene-expression profiling, is used routinely to define a risk-adapted strategy. In this disease setting, more

research is needed to identify molecular markers which could lead to advances in personalised medicine.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

Prof. Moreau has reported advisory board of Janssen, Millennium, Onyx, Celgene; speaker's honoraria from Janssen, Celgene, Mundipharma. Prof. San Miguel has reported advisory board of Millennium, Janssen, Celgene and Onyx. Prof. Mohty has reported research support and lectures honoraria from Celgene and Janssen, whose products are discussed in this manuscript. Prof. Ludwig has reported speaker's bureau honoraria from Celgene, Mundipharma, Janssen; research grants from Mundipharma, Janssen. Dr Dimopoulos has reported honoraria from Celgene, OrthoBiotech, Onyx. Prof. Dreyling has reported scientific advisory board for Celgene, Janssen, Pfizer, Roche; speaker's honoraria for Celgene, Janssen, Pfizer, Roche; research funding to the institution from Celgene, Janssen, Mundipharma, Pfizer, Roche. Prof. Schouten has declared no potential conflicts of interest.

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