REVIEW ARTICLE

The Diagnosis and Treatment of Multiple Myeloma

Christian Gerecke, Stephan Fuhrmann, Susanne Strifler, Martin Schmidt-Hieber, Hermann Einsele, Stefan Knop

SUMMARY

Background: Multiple myeloma is a malignant disease of plasma cells with a worldwide incidence of 6–7 cases per 100 000 persons per year. It is among the 20 most common types of cancer in Germany.

Methods: This review is based on pertinent publications up to December 2015 that were retrieved by a selective search of PubMed employing the terms "multiple myeloma" AND "therapy" OR "diagnostic." Systematic reviews, meta-analyses, randomized controlled trials, and treatment recommendations from Germany and abroad were considered.

Results: The diagnostic evaluation of multiple myeloma comprises thorough history-taking and physical examination, various laboratory tests including analysis of a 24-hour urine sample, a bone-marrow biopsy, and skeletal radiography. Systemic treatment should be administered only when organ damage has been diagnosed. The type of treatment to be given is chosen individually on the basis of the patient's age, comorbidities, and risk profile. High-dose therapy with autologous stem-cell transplantation remains the treatment of choice for patients under age 70 who are otherwise in good health. For patients who are not candidates for high-dose therapy or who have had a recurrence of multiple myeloma after prior high-dose therapy, there are a number of further conventional treatment options. Patients need not only systemic antineoplastic treatment, but also supportive treatment for the prevention of treatment-induced toxicity and myeloma-associated organ damage.

Conclusion: Recent therapeutic advances have made the treatment of multiple myeloma both more complex and more costly. In particular, the median survival of patients with multiple myeloma has been markedly prolonged through the use of targeted drugs such as proteasome inhibitors and immune modulators.

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Department of Hematology, Oncology, Tumor Immunology, and Palliative Medicine, Helios Hospital Berlin-Buch, Berlin: Dr. Gerecke, Dr. Fuhrmann, PD Dr. Schmidt-Hieber

Department of Medicine II, Würzburg University Hospital, Würzburg: Prof. Knop, S. Strifler, Prof. Einsele

Multiple myeloma is a systemic malignant disease of the blood, in most cases incurable. The World Health Organization (WHO) counts it among the lymphoproliferative B-cell diseases. Multiple myeloma is characterized by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow, leading to production of nonfunctional intact immunoglobulins or immunoglobulin chains. In the WHO classification, multiple myeloma is differentiated from the following plasma cell diseases (1):

- Monoclonal gammopathy of uncertain significance
- Solitary plasmocytoma of bone
- Systemic light-chain amyloidosis
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disease, and skin changes).

Epidemiology

Multiple myeloma accounts for around 1% of all cancers worldwide and 10–15% of all hematological neoplasms. In Germany there are around 6500 new cases of multiple myeloma each year and it is the third most commonly occurring disease of the blood after leukemia and non-Hodgkin lymphoma. The median age at onset is 71 years for men and 74 years for women (2). The risk of multiple myeloma is much higher in older age groups; onset before the age of 45 is rare (around 2% of cases). The relative 5-year survival rate was about 45% in the period 2009–2010. The etiology of the disease remains poorly understood. Together with ionizing radiation, pesticides and benzol, obesity and chronic infection have been postulated as factors favoring the occurrence of multiple myeloma (e1, e2).

Definition and prognostic factors

In most patients multiple myeloma develops on the basis of monoclonal gammopathy of uncertain significance, which is diagnosed, usually incidentally, in 3–5% of persons over the age of 50 years. The average risk of progression to multiple myeloma is around 1% per annum (3, 4). Another transitional phase on the way to symptomatic multiple myeloma is smoldering (asymptomatic) myeloma, which, in common with monoclonal gammopathy of uncertain significance, is characterized by the absence of organ damage (CRAB criteria) *(Table 1)*. Smoldering myeloma differs from

TABLE 1

Diagnostic criteria of the International Myeloma Working Group (e18)

	MGUS	Smoldering myeloma	Symptomatic multiple myeloma
Proportion of plasma cells in bone marrow	<10%	≥ 10%	≥ 10%
M protein in serum	<30 g/L	≥ 30 g/L	Detectable in serum and/or urine
End-organ damage (CRAB)	No	No	Present

CRAB criteria: hypercalcemia, renal insufficiency, anemia, bone lesions
MGUS, monoclonal gammopathy of uncertain significance

monoclonal gammopathy of uncertain significance, however, in its higher risk of progression to multiple myeloma. In the first 5 years after diagnosis the risk of progression is around 10% per year (5).

Smoldering myeloma does not require treatment, but therapeutic measures should nevertheless be considered in the presence of certain risk factors (e3).

The indication for initiation of treatment for multiple myeloma is essentially determined according to the CRAB criteria. In a recommendation published in 2014, the International Myeloma Working Group (IMWG) revised the criteria and extended them to symptomatic multiple myeloma. The existing criteria were supplemented by newly defined biomarkers that identify asymptomatic patients with an elevated risk of progression. These patients might be treated with the aim to avoid early end-organ damage *(Box 1)* (6).

It is unclear at present whether initiation of treatment solely on the grounds of these as yet insufficiently validated biomarkers improves the overall prognosis of patients with multiple myeloma. Further evaluation of the biomarkers in prospective randomized studies is therefore necessary because of the risk of overtreatment. The most widely used classification of multiple myeloma was developed by Durie and Salmon and introduced 40 years ago. The stage correlates with estimated tumor mass along with clinical symptoms. The prognostic significance of the findings for the individual patient is limited, however (7). The year 2005 saw the introduction of an international staging system (ISS) that is easy to apply in clinical practice, economical, and predicts the course of disease (8). Serum albumin and β2-microglobulin were identified as independent prognostic markers and form three subgroups. Stage ISS III is associated with the worst survival *(Table 2)*.

Cytogenetic changes are found in around one third of patients with multiple myeloma by conventional chromosome analysis and in over 90% when the FISH method is used (e4, e5). The genetic changes associated with a poor prognosis on FISH analysis include the immunoglobulin heavy-chain translocations t(4;14), t(14;16), and t(14;20), the 17p deletion, the 1p deletion, and amplifications of 1q. On conventional chromosome analysis the 13q deletion is also associated with an unfavorable prognosis.

Clinical features and diagnosis

The symptoms reported by patients with multiple myeloma on presentation are often non-specific and may already have been present for an extended period. Anemia of unknown origin is found in 73% of patients, bone pain in 58%, and fatigue in 32%. Around 25% of them report unexplained weight loss, and renal function is often impaired (10, e6). In addition to history taking and physical examination, the diagnostic work-up for multiple myeloma comprises clinical chemistry, cytogenetic analysis of bone marrow, and radiological investigation to detect bone changes.

For reasons of sensitivity, the conventional whole-body radiographic bone survey (the so-called Paris scheme) has largely been abandoned in favor of low-dose whole-body computed tomography. Magnetic resonance imaging and FDG positron emission tomography can be used for clarification if required. *Box 2* summarizes the investigations that are necessary for initial diagnosis of multiple myeloma (11).

First-line treatment

Patients with a clonal plasma cell disease and signs of manifest or threatened organ damage must receive adequate systemic therapy. Although this does not generally lead to cure, modern treatment plans have now increased the 5-year survival rate for myeloma patients up to 75 years of age to over 50% (12). In 3–20% of patients, complete remission can last for many years (e7, e8). In the absence of severe (cardiac and pulmonary) comorbidities, the standard treatment in Germany remains high-dose melphalan (200 mg/m^2) followed by retransfusion of autologous blood stem cells (13). The upper age limit of 65 or 70 years is determined not so much by age per se as by medical fitness and regulations. The treatment begins with induction chemotherapy. The principal active substances are the proteasome inhibitors Velcade (bortezomib) and dexamethasone (the VD protocol). In most cases, however, Velcade (bortezomib) and dexamethasone are combined with cyclophosphamide or adriamycin, or alternatively with thalidomide (VTD), for the sake of improved efficacy. In August 2013 the European Medicines Agency extended the indication for bortezomib to cover non-pretreated patients before planned high-dose treatment and stem cell transplantation. After three to

BOX 1

Definition of symptomatic multiple myeloma according to the revised IMWG criteria (6)

- Clonal plasma cells in bone marrow ≥ 10% or biopsy-confirmed bone plasmocytoma or an extramedullary manifestation and one of the following myeloma-defining events:
- CRAB criteria
  - Hypercalcemia: serum calcium >0.25 mmol/L above upper limit of normal range or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: GFR <40 mL/min or serum creatinine >177 µmol/L
  - Anemia: >2.0 g/dL under lower limit of normal range or <10 g/dL
  - Bone lesions: ≥ 1 lesion detected by radiography, computed tomography or positron emission tomography
- Biomarkers
  - Clonal plasma cells in bone marrow ≥ 60%
  - Ratio of involved/uninvolved free light chains (FLC) ≥ 100
  - >1 focal lesion >5 mm on MRI

GFR, glomular filtration rate; IMWG, International Myeloma Working Group; MRI, magnetic resonance imaging
CRAB criteria: threshold values in multiple myeloma for assessment of disease consequences: C, calcium elevation in blood, R, renal insufficiency; A, anemia; B, bony lesions

six cycles of induction therapy, 75–80% of patients achieve a partial remission (14–16). The induction therapy used for this indication in the USA, combining the immunomodulatory substance lenalidomide with dexamethasone, has not received European approval for use in patients suited for transplantation.

In 2014 an Italian study group published the results of a trial comparing a tandem high-dose protocol (two courses of high-dose melphalan) with conventional treatment (six cycles of melphalan/prednisone and lenalidomide. The time that elapsed before the next occurrence of disease activity or death (progression-free survival) was a median 20 months longer in the high-dose group. Overall survival after 4 years was 82% for the high-dose group versus 65% in the conventionally treated group (17). Whether, in view of more effective induction regimens, single or tandem high-dose treatment is preferable remains to be established by prospective randomized controlled trials. The guidelines are inconsistent in this respect. The value of a second course of high-dose treatment in the event of insufficient response (i.e., failure to achieve complete remission) is broadly accepted. Combined autologous/allogeneic stem cell transplantation has been shown to be advantageous in patients at very high risk (17p deletion, extramedullary disease) (Knop et al.: Autologous followed by allogeneic versus tandem-autologous stem cell transplant in newly diagnosed FISH-del13q myeloma. Blood 2014; 124: abstract 43).

Concepts for improvement or maintenance of remission are being investigated in the attempt to delay recurrence of multiple myeloma. Cytostatic drugs, steroids, interferon, and also thalidomide have been tested but largely abandoned owing to significant adverse effects and, in some cases, lack of sufficient efficacy. In several studies administration of lenalidomide up to the time of first progression has been shown to prolong progression-free survival (17–19). Because of an increased incidence of secondary malignancies, inconsistent results with regard to prolongation of overall survival, and the lack of approval by licensing authorities in Germany, maintenance treatment with lenalidomide has not yet become standard.

Given its short duration and its potential to achieve extended progression-free interval, high-dose treatment should also be considered as a first-line treatment for patients aged 65 to 75 years whose cognitive and physical status is good. Although administration of 200 mg/m^2 as standard dose for patients over 70 has been reported, a dose of 140 mg/m^2 can reduce toxicity. The adverse effects seem to increase sharply from the age of 65 upward, and only small numbers of patients have been treated with the standard dose (20, e9, e10). Comprehensive evaluation with regard to comorbidities and cognitive and physical status may help to establish a patient's suitability for intensive forms of treatment as well as the adverse effects that are apt to occur (21). A randomized controlled trial by the German Multiple Myeloma Study Group (*Deutsche Studiengruppe Multiples Myelom*) is close to completion. This study compares long-term administration of lenalidomide/dexamethasone with tandem high-dose (140 mg/m^2) melphalan.

So-called conventional therapy is the treatment of choice for patients over 75 years of age.

A randomized controlled trial published in 2007 showed that melphalan and prednisolone (MP) plus thalidomide (MPT) was superior to MP alone or greatly attenuated high-dose treatment with regard to progression-free survival and overall survival (22). As a result, the MPT protocol was licensed for this indication. A year later, the results of another randomized controlled trial appeared: the combination of prednisolone and bortezomib showed clear superiority of the VMP protocol (bortezomib, melphalan, prednisone) over the standard treatment in all time-related endpoints (23).

In this first generation of studies, however, the high degree of efficacy was associated with high rates of discontinuation due to toxicity. For this reason, alternative ways of administering bortezomib were developed (e.g., once instead of twice weekly; subcutaneous instead of intravenous). Lenalidomide is more effective than thalidomide, but causes more hematological adverse effects. In a protocol no longer including melphalan, it was shown that lenalidomide could be successful in treating older patients: the French study group compared continuous administration of lenalidomide and dexamethasone up to the

time of first progression with 18 cycles of lenalidomide and dexamethasone and with the standard of 12 cycles of melphalan, prednisone, and thalidomide (24). Both progression-free survival and overall survival were better in the experimental arm of the study than with the hitherto standard treatment. Modified bortezomib, melphalan, prednisone (nine cycles) and continuous lenalidomide and dexamethasone until progression is detected are the first-line treatments of choice in patients for whom high-dose treatment ist not an option. Direct comparison of these two regimens would be desirable to determine whether one is superior to the other. *Figure 1* shows a treatment algorithm for patients with newly diagnosed multiple myeloma that requires treatment.

TABLE 2

International Staging System

Stage	Laboratory parameters	Median survival (months)
I	Serum albumin ≥ 35 g/L β2-microglobulin <3.5 mg/L	62
II	Neither I nor III	44
III	β2-microglobulin >5.5 mg/L	29

Treatment of recurrences

The treatment of recurrent/refractory (r/r) multiple myeloma depends on age, comorbidities, and previous treatment. The best time to begin treatment is keenly debated. If paraprotein is increasing slowly, initiation of treatment can be delayed, but therapy should be initiated immediately in the presence of new myeloma-related organ damage and/or a rapid increase in paraprotein (25). Patients with recurrent multiple myeloma whose general condition is good with no serious comorbidities can receive high-dose treatment with melphalan together with autologous stem cell transplantation (e11–e13).

Proteasome inhibitors, immunomodulatory substances, and classical chemotherapy agents play a crucial role in the treatment of recurrent multiple myeloma.

The proteasome inhibitor bortezomib is among the substances most frequently used in patients with r/r multiple myeloma (26). Bortezomib combined with corticosteroids or other substances (e.g., bendamustine) has been tried in treatment of recurrences (27). Clinical trials have shown that bortezomib can be efficacious even in patients previously treated successfully with this substance (28). Novel proteasome inhibitors, e.g., carfilzomib and ixazomib, have also achieved promising results in various combinations in patients with (r/r) multiple myeloma (e14). A recently published randomized controlled trial showed better progression-free survival in patients with (r/r) multiple myeloma who received carfilzomib in combination with lenalidomide and dexamethasone than in those treated with lenalidomide and dexamethasone alone (e15). On that basis this combination treatment was licensed for use in (r/r) multiple myeloma in December 2015 (e15).

Lenalidomide and pomalidomide are among the immunomodulatory drugs approved for use in (r/r) multiple myeloma. Two large randomized controlled trials demonstrated that treatment with lenalidomide and dexamethasone is very effective, achieving significantly better overall survival than dexamethasone alone in patients with recurrent multiple myeloma (29).

Pomalidomide was licensed on the basis of a randomized controlled trial that compared pomalidomide plus low-dose dexamethasone with high-dose dexamethasone in patients with r/r multiple myeloma (30).

Bendamustine, doxorubicin, cyclophosphamide, and melphalan are also frequently used in the treatment of r/r multiple myeloma, mostly in combination with corticosteroids and/or one of the newer substances.

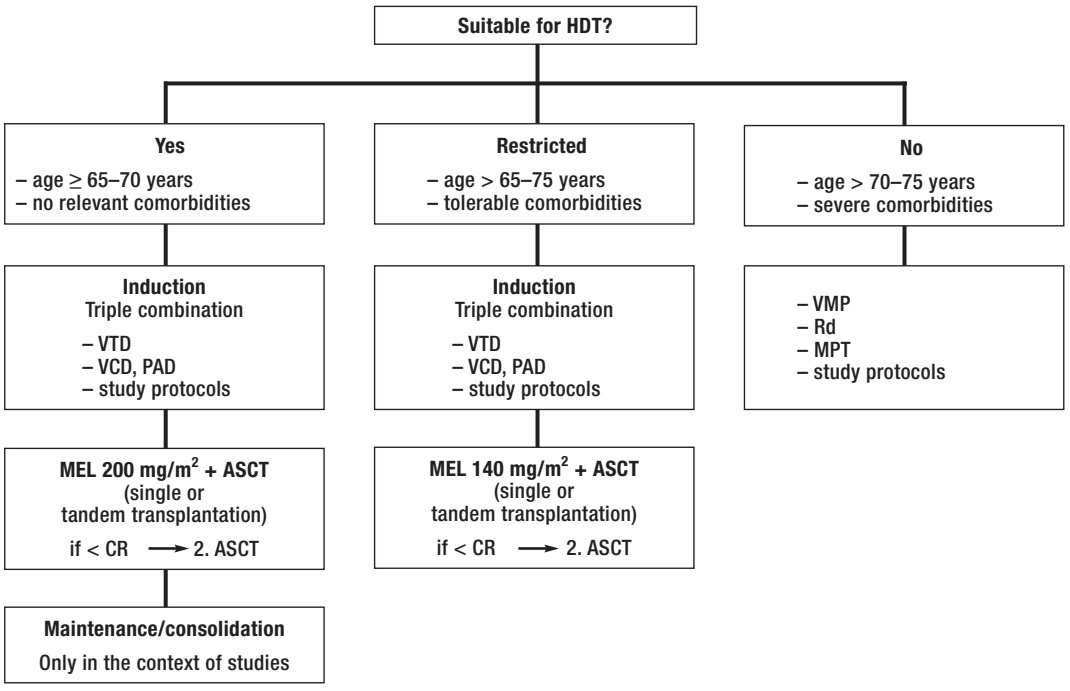
Numerous novel substances with various mechanisms of action are currently undergoing investigation in clinical trials for their efficacy against r/r multiple myeloma. The anti-CS1-(SLAMF7) antibody elotuzumab and the histone-deacetylase inhibitor panobinostat are among the substances at the forefront of clinical development. In a study that investigated lenalidomide plus dexamethasone with and without elotuzumab, patients treated with elotuzumab showed significantly

BOX 2

Diagnosis of multiple myeloma

- Laboratory parameters in serum
  - Differential blood count, electrolytes, creatinine, LDH, CrP, β2-microglobulin
  - Plasma coagulation, total protein, albumin
  - Serum electrophoresis with densitometric determination of M protein
  - Quantitative determination of immunoglobulins (IgG, IgA, IgM, IgD)
  - Determination of free light chains (including FLC ratio), immunofixation electrophoresis
- Laboratory parameters in urine
  - 24-h urine collection, determination of free light chains
  - Immunofixation electrophoresis, albumin
- Bone marrow diagnosis
  - Cytology and/or histology, cytogenetic investigation (chromosome analysis and FISH) to detect unfavorable cytogenetic aberrations
- Diagnostic imaging
  - Low-dose whole-body computed tomography
  - Supportive magnetic resonance imaging, positron emission tomography if needed

FIGURE 1



Risk-adjusted treatment algorithm for newly diagnosed patients with multiple myeloma requiring treatment

MEL, melphalan; MPT, melphalan, prednisone and thalidomide; PAD, Velcade (bortezomib), adriamycin, dexamethasone; Rd, lenalidomide, dexamethasone; VCD, Velcade, cyclophosphamide, dexamethasone; VMP, Velcade, melphalan, prednisolone; VTD, Velcade, thalidomide, dexamethasone;
ASCT, autologous stem cell transplantation; CR, complete remission; HDT high-dose treatment

longer progression-free survival (31). Detailed analyses of overall survival have yet to be published. On 3 September 2015 the European Medicines Agency approved the histone-deacetylase inhibitor panobinostat in combination with bortezomib and dexamethasone for treatment of previously treated multiple myeloma (32). Elotuzumab has recently been licensed for treatment of recurrent multiple myeloma in Germany.

Supporting treatment

Supportive therapy comprises the management of the complications of myeloma and the adverse effects of the drugs used for treatment. These include above all pain as a result of skeletal lesions (osteolyses and fractures), peripheral neuropathy, infection as a consequence of neutropenia and/or antibody deficiency, hypercalcemia, and venous thromboembolism.

Pain is treated according to the well-known WHO pain relief ladder (33). If non-steroidal anti-inflammatory drugs (NSAIDs) are given, the frequently impaired renal function should be closely monitored (34). In addition, osteolyses—generally the lead symptom—are usually irradiated, as are soft-tissue plasmocytomas (34). To delay further skeletal events, reduce pain, and correct hypercalcemia, regular administration of a bisphosphonate (pamidronate, zoledronate, or clodronate) is initiated in parallel with systemic treatment (35). Before bisphosphonate treatment is started, careful assessment of the dental status is mandatory to avoid bisphosphonate-associated osteonecrosis of the jaw (36). Treatment for 2 years is recommended, but can be ended after 1 year if full remission or very good partial remission has been achieved. In the case of less favorable response bisphosphonate administration can be continued, but in view of the absence of clinical data the advisability of treatment beyond 2 years must be weighed up carefully (37, 38).

Symptoms caused by peripheral neuropathy may occur as an adverse effect of treatment with bortezomib and thalidomide, necessitating dose reduction or treatment modification (37). Preventive medication is not possible; supportive measures include physical therapy, tricyclic antidepressants, and anticonvulsives (e.g., gabapentin or pregabalin) (37).

Infections are the principal cause of death among patients with multiple myeloma. Despite the elevated risk of infection, routine administration of prophylactic antibiotics is not recommended; they can be given,

however, on an individual basis in particular situations (prolonged neutropenia, repeated infectious complications) (34). High numbers of infections have also been observed in the initial phase of treatment with immunomodulatory substances, and these patients might also benefit from being given prophylactic antimicrobials (e16). In the case of prolonged neutropenia or recurring bacterial infections, granulocyte-colony stimulating factors (G-CSF) and intravenous immunoglobulins can be prescribed. Administration of aciclovir to prevent shingles is a necessary accompaniment of bortezomib treatment and should be continued for 6 weeks after the last dose of bortezomib (39). Both high-dose treatment and higher doses of steroids (>20 mg prednisolone equivalent/day for 4 weeks for more) should be followed by co-trimoxazole (if not tolerated, inhaled pentamidine) to prevent *Pneumocystis* pneumonia.

Patients with multiple myeloma are at increased risk of venous embolism. The incidence lies between 8 and 22 per 1000 patients per year (e17). The risk is influenced by patient-specific factors (immobility, hyperviscosity, previous venous thrombosis) and is increased by treatment with immunomodulatory substances or high-dose steroids (>480 mg dexamethasone/month) (36). Prophylactic administration of acetylsalicylic acid, low-molecular heparin, or vitamin K antagonists, depending on the number of risk factors, is mandatory (40).

KEY MESSAGES

- Multiple myeloma is a malignant systemic hematological disease that arises from monoclonal plasma cells. It usually affects older patients and is characterized by the presence of monoclonal immunoproteins in the serum and/or urine.
- The indication for treatment is based on the demonstration of organ damage (as assessed using the CRAB criteria) and recently defined biomarkers.
- The diagnostic work-up comprises mandatory analysis of blood and urine samples, bone marrow evaluation, and imaging procedures.
- In patients under 70 years of age without serious comorbidities, induction treatment should be followed by high-dose treatment with autologous stem-cell transplantation. Older patients can be managed with age-adjusted high-dose treatment and autologous stem-cell transplantation or with one of the various established medical treatment options. Supportive measures such as pain therapy, administration of bisphosphonates, and irradiation of skeletal/extramedullary lesions are important accompaniments to the antineoplastic treatment of patients with multiple myeloma.

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Corresponding author
Dr. med. Christian Gerecke
Klinik für Hämatologie, Onkologie, Tumorimmunologie und Palliativmedizin
HELIOS Klinikum Berlin-Buch
Schwanebecker Chaussee 50, 13125 Berlin, Germany
christian.gerecke@helios-kliniken.de

Supplementary material
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