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REVIEW

International Myeloma Working Group recommendations for global myeloma care

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Recent developments have led to remarkable improvements in the assessment and treatment of patients with multiple myeloma (MM). New technologies have become available to precisely evaluate the biology and extent of the disease, including information about cytogenetics and genetic abnormalities, extramedullary manifestations and minimal residual disease. New, more effective drugs have been introduced into clinical practice, which enable clinicians to significantly improve the outcome of patients but also pose new challenges for the prevention and management of their specific side effects. Given these various new options and challenges, it is important to identify the minimal requirements for diagnosis and treatment of patients, as access to the most sophisticated advances may vary depending on local circumstances. Here, we propose the minimal requirements and possible options for diagnosis, monitoring and treatment of patients with multiple myeloma.

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INTRODUCTION

Multiple myeloma is the second-most common cancer of the blood and accounts for 1% of all malignancies. Extrapolating these figures to the estimated incidence of cancer yields a global incidence of roughly 120 000 cases per year. With a median age of 70 years at diagnosis and a rapidly aging world population, these figures likely will rise significantly to about 350 000 cases by the year 2050. Although age-standardized incidence rates vary with ethnicity from 3.9/100 000 in Chinese to 12.7/100 000 in African individuals (SEER data),[1] the figures indicate that multiple myeloma (MM) poses a substantial global health problem.

During recent years, many improvements in our understanding of the biology[2] and in the management of the disease have been made.[3] Although the basic criteria for establishing a diagnosis have not changed since the first descriptions in the early sixties,[4] the techniques available for assessing the cytogenetic and genetic characteristics and for the evaluation of bone and soft tissue manifestations of the disease have been improved significantly. Staging and prognostication[5] can be upgraded by complementing the International Staging System with additional investigations, such as positron emission tomography, magnetic resonance imaging and cytogenetics.[6] The treatment has been markedly improved with the introduction of a first wave of novel agents and will continue to be developed further, with many trials investigating agents with new modes of action currently ongoing.[7] Improvement in supportive care has led to a more sophisticated symptom control and has saved many lives by better prophylactic strategies and more efficient management of complications of the disease and of therapy.

Given the plethora of novel developments, the issue of minimal requirements for the management of this complex disease becomes highly relevant. The IMWG convened at the occasion of the European Hematology Association meeting in Amsterdam in June 2012 to address, among various other topics, this important issue. The current manuscript contains the summary and recommendations of the working group on 'Global Myeloma Care' and represents an international perspective, with the aim of providing relevant information and recommendations for clinicians across the globe. Because of substantial differences in healthcare systems, approval status of different agents, and economic constraints, the recommendations given may not always be feasible. With this consideration in mind, alternative options have been provided where possible.

ESTABLISHING A DIAGNOSIS OF ACTIVE MULTIPLE MYELOMA

The diagnosis of MM is based on the presence of monoclonal plasma cells, monoclonal protein and myeloma-related organ and tissue impairment including bone lesions.[8] Monoclonal plasma cells must be documented in all patients, whereas myeloma-

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specific bone lesions are detected in about 80% of patients at the time of diagnosis and 1–3% of patients present with oligo- or nonsecretory myeloma. Of note, MM must be distinguished from MGUS and smoldering myeloma and other variants of clonal plasma cell expansion need to be considered, such as solitary plasmacytoma of the bone with or without detectable dissemination of monoclonal cells, extramedullary plasmacytoma, primary amyloidosis and light-chain deposition disease.

A diagnosis of monoclonal plasma cell proliferation is usually made by bone marrow aspiration and/or bone marrow biopsy. Both techniques are recommended, although bone biopsy is not considered essential by some experts. Bone marrow aspiration offers the advantage of further characterization of the monoclonal cell population by immunophenotyping, fluorescence in situ hybridization, cytogenetics and conventional karyotyping. Fluorescence in situ hybridization using probes for poor-risk abnormalities that include del17p13, t(4; 14), t(14; 16), amplification 1q21 and del 1p, as well as conventional karyotyping, which enables a separation between hypodiploid and hyperdiploid myeloma, offer prognostic information.[9] However, neither these tests nor immunophenotyping is considered mandatory at present. A bone biopsy provides more accurate information about the degree of bone marrow infiltration, other bone marrow cells and, in addition, allows the immunophenotypic characterization of plasma cells. It is also a useful baseline for future comparison. The absolute minimal requirement is bone marrow aspiration and, in case of solitary plasmocytomas, fine needle aspiration, although a histological specimen is preferred.

For the detection and characterization of monoclonal immunoglobulin, both serum and urine need to be assessed. In more than 80% of patients, a monoclonal paraprotein will easily be detected using serum electrophoresis, but in 16–18% of cases only free light chains can be detected either in serum[10] and urine or in urine only, and in a few patients monoclonal proteins can be detected neither in serum nor in urine. All patients should have a serum protein electrophoresis, a urine protein electrophoresis of a 24-hour urine specimen (if needed of a concentrate), immunofixation in serum and urine, as well as determination of serum free light-chains and their ratio. Quantification of serum paraproteins may be hampered or impossible by serum protein electrophoresis when myeloma proteins co-migrate with other proteins such as transferrin, ß-lipoprotein and C3 toward the anodal region, making nephelometry the preferred method, particularly in patients with IgA M-proteins.

A whole skeletal bone survey by conventional radiography, including the spine, skull, shoulders, thoracic cage, pelvis and long bones of arms and legs, is still considered standard for the initial workup. Results of the conventional bone survey are needed to apply the staging system described by Durie and Salmon,[11] and are used in many clinical studies for the evaluation of bone disease. It also provides an evaluation for the risk of imminent pathological fracture, which may require radiotherapeutic or surgical intervention. Newer techniques, such as computed tomography, magnetic resonance imaging and positron emission tomography, have greatly increased the sensitivity for the detection of myeloma-specific bone lesions. The former two techniques can either be used to evaluate specific areas of interest or for whole-body scanning. Combining those methods with positron emission tomography seems to be particularly useful for the detection of extra-skeletal masses, but the routine use of these techniques is not recommended at present.[12] Clinicians need to be aware that osteoporosis may be the only bone finding in myeloma, and usually it is not possible to distinguish myeloma-induced osteoporosis form bone loss due to other causes.

The following additional laboratory tests are required for the assessment of the extent and level of activity of the disease: Albumin and ß2-microglobulin are needed for International Staging System. In addition, an analysis of the complete blood count, as well as of the levels of calcium, creatinine and lactate dehydrogenase, is recommended. A determination of C-reactive protein levels is not mandatory, but may be helpful when an infection is suspected. The same applies to vitamin D levels, which are decreased in about 20% of myeloma patients.[13]

In addition, both myeloma and host-related issues need to be considered. An assessment of the overall state of the patient, including age, performance status, organ function (renal, cardiovascular, bone marrow, pulmonary, cognitive) and dental evaluation, will help identify potential comorbidities and guide treatment decisions. Table 1 contains a summary of essential procedures to establish a diagnosis of MM.

PARAMETERS FOR THE INITIATION OF THERAPY

Treatment should be initiated in all patients with active myeloma fulfilling the CRAB criteria, namely presenting with one or more of clinically relevant bone lesions, anemia (Hb $<$ 10 g/dl), myeloma-induced renal impairment (creatinine $>$ 2.0 mg/ml) and hypercalcemia ($>$ 11.0 mg/dl), as well as in those symptomatic owing to the underlying disease. In patients with smoldering MM historical, small randomized trials comparing an early initiation of treatment with a deferred start once patients became symptomatic or otherwise at risk for severe myeloma-induced complications were unable to show a survival advantage for an early onset of therapy. This standard is presently being challenged by data from a Spanish trial showing a significant prolongation of progression-free and overall survival (OS) in patients with high-risk smoldering myeloma subjected to immediate, as compared with deferred, myeloma therapy.[14] For the time being, and before results have been confirmed by other trials, starting treatment when patients become symptomatic because of myeloma and/or fulfill the CRAB criteria is considered standard, although initiation of therapy may also be considered for prevention of imminent disease-related complications such as increasing deterioration of renal function, but not having reached the cutoff level of 2 mg/dl creatinine.

MONITORING

Patients on treatment should be carefully monitored for response to therapy, for symptoms of their disease and for any toxic sequels of therapy. After the initiation of therapy, patients should be monitored monthly, or more frequently if clinically indicated, whereas during follow-up or maintenance the frequency of monitoring can be reduced to every 2–3 months. In addition to clinical evaluation, the following should form a part of routine monitoring: a full blood count, creatinine and/or glomerular filtration rate, calcium, albumin, lactate dehydrogenase, M-protein quantification using electrophoresis and nephelometry for IgA paraproteins, keeping in mind that in IgG and in the rare case of IgM myeloma the amount of paraprotein may be overestimated by nephelometry.[15] The serum free light-chains should be measured particularly in patients with oligo- or nonsecretory MM. An increase in the involved free light-chain accompanied by changes in the serum free light-chains ratio indicates progressive disease. This refers also to patients with light-chain escape, where progressive disease is not reflected in changes in the heavy-chain level. Twenty-four-hour urine M-protein excretion should be included in case of light-chain myeloma and measurable urine spike, as well as in patients with suspected renal amyloidosis or light-chain escape. Monthly assessment of serum and urine protein is recommended during active therapy, but intervals can be prolonged markedly once the disease enters a plateau phase when the decision regarding the frequency of assessment should be left at the discretion of the treating physician. Response should be evaluated according to the criteria issued by the IMWG[16,17]

Table 1. Essential procedures for the diagnosis and follow-up of multiple myeloma

Parameter of interest		Information provided
Monoclonal plasma cells		
Bone marrow aspiration and/or bone biopsy	Baseline	BMPC infiltration, enables FISH cytogenetics, immunophenotyping, immunocytochemistry, conventional karyotyping, gene arrays
	Follow up	For documentation of CR and of PD
Monoclonal protein		
Serum electrophoresis	Baseline	M-component, possible suppression of non-paraprotein immunoglobulins; emergence of a new M-component (rare)
	Follow up	Regularly when M-component detectable and in longer intervals in initially serum M-component negative patients
Urine electrophoresis (24-hour urine)	Baseline	M-component, indicates glomerular damage when albumin present (amyloidosis).
	Follow up	Regularly when urine M-component detectable and in longer intervals in initially urine M-component negative patients
Nephelometry of serum immunoglobulins	Baseline	Measurement of IgA, overestimates the M-component concentration in patients with IgG and IgM myeloma. Provides information about suppression of non-involved immunoglobulins
	Follow up	Regularly when M-component (IgA) detectable and in longer intervals in initially serum M-component negative patients
Immunofixation electrophoresis	Baseline	Identifies isotype and light chain type, confirms CR at baseline in serum and in urine in those with proteinuria
	Follow up	For confirmation of CR and for early detection of reappearance of the M-component
Free light chain Measurement (Serum)	Baseline	M-component in patients with light chain and oligo secretory myeloma, supports disease monitoring in all patients
	Follow up	For monitoring of disease, particularly in those with light chain or oligo secretory myeloma
Myeloma specific bone lesions		
Skeletal bone survey by conventional radiography	Baseline	Assessment of extent of bone disease, and of progressive bone disease
	Follow up	During FU in those with suspected new bone disease
CT, MRI, PET, PET/CT, PET/MRI	Baseline	Higher sensitivity for myeloma specific bone lesions Assessment of extramedullary disease, PET provides information about activity of the disease
	Follow up	Presently only recommended for detection of extramedullary disease or suspected spinal cord compression
Additional laboratory parameters		
Albumin, β2-microglobulin, blood count, calcium, creatinine, LDH, total protein, , Liver function tests (CRP, vitamin D, not obligatory)	Baseline	Provides information about organ function and aggressiveness of the disease (LDH), bacterial infections (CRP)
	Follow up	

Abbreviations: CT, computed tomography; CR, complete response; CRP, C-reactive protein; FISH, fluorescence in situ hybridization; FU, follow-up; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PD, progressive disease; PET, positron emission tomography.

and, if minor response should be evaluated in the relapsed/refractory setting, by the definition released by the EBMT group.[18]

The bone marrow should be assessed as a routine by aspirate and/or biopsy at the time of a suspected complete response, usually at complete disappearance of the monoclonal component. In nonsecretory MM, the assessment of the bone marrow is required to evaluate the quality of response. For transplant patients 2–4 months after autologous stem cell transplantation (ASCT) and for conventionally treated patients 4–6 months after start of therapy may be appropriate time points. During follow-up, re-biopsies should be scheduled individually and be performed whenever the patient becomes symptomatic or if bone marrow failure develops, whereas in asymptomatic patients without new bone lesions and laboratory abnormalities (normal hemoglobin, renal function, calcium and lactate dehydrogenase levels) biopsies can be withheld.

A skeletal survey using radiography or magnetic resonance imaging or computed tomography in case of plasmacytoma, extramedullary disease or a suspected spinal cord compression is generally recommended.[19] During active therapy, a skeletal survey should be conducted only at the time of the appearance of new skeletal-related symptoms or suspected progressive disease using appropriate imaging techniques. It is important to select the technique that is most suited for the investigation of particular symptoms. Nevertheless, the same

imaging technique should be used to assess new lytic lesions in order to make appropriate comparisons with the baseline data. Initial results indicate a significant prognostic impact of negative positron emission tomography findings after a given number of chemotherapy cycles.[20]

TREATMENT

Transplant-eligible patients

Patients deemed eligible for ASCT should be treated with 3–4 cycles of active induction therapy, followed by stem cell collection and high-dose therapy with stem cell transplantation. Of note, studies aimed at elucidating the optimal number of cycles before high-dose therapy are not available, and trials using more than four cycles have been reported.[21] In case of a suboptimal response (less than PR) to four cycles of induction therapy, it is recommended to proceed to stem cell transplantation without modification of the original treatment plan, as the transplant procedure is known to upgrade responses.[22] In case of progressive disease after the first two–three cycles, a change of the type of the induction regimen seems indicated, but the benefit of this approach has not formally been proven.

The most active regimen available should be used for induction therapy (Table 2). This should include novel drugs. Several studies showed superiority of a three-drug, bortezomib-based regimen over VAD or two-drug combinations, rendering it the preferred combination for induction therapy.[21,23–30] In countries where bortezomib is not available for frontline therapy, the use of the CTD regimen (cyclophosphamide + thalidomide + dexamethasone) is an option.[29] Two-drug regimens with bortezomib–dexamethasone, lenalidomide–dexamethasone or thalidomide–dexamethasone may also be used, although the latter regimen was found to be markedly inferior to a VTD combination.[21,23] In case neither a bortezomib-based regimen nor CTD or lenalidomide + dexamethasone regimens are feasible, VAD may be a regimen of choice in selected situations and individual countries, if no other options are available.

The conditioning for the transplant procedure should be carried out with melphalan 200 mg/m^2 (MEL200). Attempts to improve the efficacy of the conditioning regimen by adding busulfan[31] or a limited number of bortezomib doses[32] to MEL200 have been reported, but these regimens cannot be considered standard as yet. In general, one transplant procedure should be conducted; however, it is recognized that tandem transplant forms part of routine practice in some centers, improves response rates[33,34] and may benefit patients with inferior response to a single transplant[27] and also those with high-risk cytogenetics.[35]

Taken together, the absolute minimum in case of no other options is four cycles of VAD followed by high-dose melphalan and ASCT. At present, a three-drug regimen incorporating bortezomib followed by one course of high-dose therapy and ASCT is recommended.

Frontline nontransplant setting

Recommended treatments for patients not eligible for high-dose therapy, or in case the transplant procedure is not available, include MPT, MPV and CTD, on the basis of the results of phase 3 studies that have demonstrated the superiority of these regimens over conventional chemotherapy (Table 3).[36–38] Longer progression-free survival (PFS) has also been shown for frontline bendamustine–prednisone compared with MP therapy,[39] but, although approved in Europe, the regimen is only rarely used for frontline treatment. Therapy should be administered until best response for 9–12 cycles. In addition, other regimens such as VCD or VTD and the use of two-drug regimens, such as VD, vD, LD and TD, present effective options. The doses of dexamethasone and the other agents have to be adapted according to age and tolerance. Bortezomib should be given subcutaneously, and a weekly schedule is an attractive alternative over the standard twice-weekly schedule. However, the panel is aware that accessibility to these treatments will vary geographically and will be influenced by economic situations. Furthermore, the panel recognizes that MP can be a useful option for patients with good-risk disease, as well as in those who have no or only minor symptoms when novel agents are not available. In addition, it is acknowledged that new drugs such as carfilzomib are currently being incorporated into first-line treatments and compared with the established therapies. Preliminary results from ongoing trials indicate that they may supersede the activity of their class-specific counterparts.

Elderly unfit and frail patients

Scientific data are scarce in this growing subset of patients. Comorbidity correlates with age and with poor prognosis,[40–42] and patient status should carefully be assessed before treatment selection. Elderly myeloma patients should be categorized as 'fit,' 'unfit' or 'frail'.[43] Treatment needs to be adapted accordingly; two-drug combinations improve tolerance often without jeopardizing activity[44] and drugs doses should carefully be tapered to the biological status of the patients.[45]

In summary, MP is the minimum that should be offered, but it has to be acknowledged that it will be suboptimal particularly for patients with poor risk cytogenetics or other poor risk features. A regimen adding a novel drug to the MP backbone or a bortezomib- or lenalidomide-based regimen is recommended.

Table 2. Regimens for induction therapy before high-dose chemotherapy and stem cell transplantation

Main components	Preferred option – 3-drug, bortezomib-based regimens	2-drug regimens	4-drug regimens
Bortezomib-based	PAD, VCD	VD	
Bortezomib+IMiD-based	VRD, VTD		VRDC, VDTC
Lenalidomide-based		LD, Ld	
Thalidomide-based	TAD, CTD	TD	
If none of the novel drugs available	VAD		

Abbreviations: CTD, cyclophosphamide with thalidomide plus dexamethasone; LD, lenalidomide with high-dose dexamethasone; Ld, lenalidomide with low-dose dexamethasone; PAD, bortezomib with adriamycin plus dexamethasone; TD, thalidomide with dexamethasone; TAD, thalidomide with adriamycin plus dexamethasone; VCD, bortezomib with cyclophosphamide plus dexamethasone; VD, bortezomib with dexamethasone; VRD, bortezomib with lenalidomide plus dexamethasone; VTD, bortezomib with thalidomide plus dexamethasone; VRDC, bortezomib with lenalidomide plus dexamethasone plus cyclophosphamide; VDTC, bortezomib with dexamethasone plus thalidomide plus cyclophosphamide; VAD, vincristine with adriamycin plus dexamethasone.

Table 3. Regimens for induction therapy for patients not eligible for high-dose therapy and stem cell transplantation

Main components	Preferred option–3 drug, melphalan-or cyclophosphamide-based regimens	2-drug regimens	4-drug regimens
Thalidomide	MPT, CTD	TD	
Bortezomib	MPV, VCD	VD, vD	VMPT
Thalidomide & Bortezomib	VTD		
Lenalidomide		LD, Ld	
If none of the novel drugs available		MP, BP	

Abbreviations: BP, bendamustine plus prednisone; CTD, cyclophosphamide with thalidomide plus dexamethasone; LD, lenalidomide with high-dose dexamethasone; Ld, lenalidomide with low-dose dexamethasone; MPT, melphalan with prednisone plus thalidomide; MPV, melphalan with prednisone plus bortezomib; MP, melphalan with prednisone; TD, thalidomide with dexamethasone; VCD, bortezomib with cyclophosphamide plus dexamethasone; VD, bortezomib with dexamethasone; vD, reduced-dose bortezomib with dexamethasone; VMPT, bortezomib with melphalan plus prednisone plus thalidomide; VTD, bortezomib with thalidomide plus dexamethasone.

Consolidation and maintenance therapy

Consolidation treatment is defined as an intensive therapy administered for a limited period of time with the main intent of improving the quality of the response and thereby OS. At present, results obtained with bortezomib, lenalidomide–bortezomib–dexamethasone (VRD), lenalidomide–dexamethasone and VTD or TD are available.[46–50] Twenty doses of bortezomib given during 21 weeks after ASCT resulted in a significant prolongation of PFS, but a survival gain was not observed.[49] The PFS benefit was only noted in patients with less than VGPR before start of consolidation treatment. Consolidation with VTD after ASCT increased the proportion of patients with PCR-defined molecular remission (minimal residual disease (MRD) negativity).[51] Patients who achieved MRD negativity had a significantly increased PFS, which possibly will translate into longer OS. Nevertheless, as survival data are not yet available, a definite recommendation for the routine use in clinical practice cannot be given at present, but in spite of these facts consolidation is increasingly being used.

Maintenance therapy is started after a successful induction therapy and/or after consolidation therapy, and aims to prolong the time of remission with a good quality of life, with the ultimate goal of improving OS. Thalidomide maintenance therapy after autologous transplantation improved PFS in all six trials and OS in 3/6 studies,[52–57] but tolerance of the agent is a limiting factor. In elderly patients, an improvement in PFS without any benefit for OS has been found with thalidomide maintenance therapy.[55–58] Importantly, thalidomide maintenance therapy was even associated with inferior OS in high-risk patients.[55] Bortezomib has been used as sole therapy or in combination with thalidomide after ASCT[21,26] and in combination with thalidomide or with prednisone in elderly patients.[59,60] When bortezomib was used in transplant-eligible patients both for induction and maintenance, a significant improvement in PFS and OS was noted as compared with thalidomide, but the design of the trial does not allow for a clear evaluation of the role of bortezomib in the maintenance setting.[26] The combination of bortezomib plus thalidomide resulted in a superior PFS compared with thalidomide or interferon maintenance therapy alone in younger patients.[21] In elderly patients, bortezomib plus thalidomide maintenance was found to yield a longer PFS compared with bortezomib plus prednisone, but, so far, the survival in both groups is comparable.[59] VMPT followed by VT yielded a longer PFS and OS compared with sole VMP induction therapy in elderly patients, but the impact of VT maintenance in this study is difficult to assess owing to the design of the trial.[60]

Lenalidomide maintenance has been evaluated in elderly patients in one trial[61] and in younger patients in three trials.[46,62,63] All four studies showed a striking improvement in PFS with lenalidomide maintenance therapy, but OS was superior in only two of the three trials conducted in younger patients.[62,63]

Lenalidomide maintenance treatment is associated with a roughly threefold increased incidence of secondary primary malignancies,[64] but when the risk for dying is analyzed in patients with and without lenalidomide maintenance the odds for lower mortality are clearly in favor of patients on lenalidomide maintenance. Still, at the current time, the panel does not recommend the routine use of maintenance therapy.[65]

Treatment of relapsed and refractory disease

Relapse of myeloma (defined as an increase in the monoclonal protein by more than 25% and >0.5 g/dl) can evolve slowly without clinical signs or symptoms or fast with or without clinical complications. Treatment is required in those with symptoms and/or imminent complications. Selection of therapy depends on patient-specific factors, tumor characteristics, such as cytogenetics, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval from the last therapy.[66,67] Drugs with potential neurotoxicity, such as bortezomib or thalidomide, should be avoided in patients with polyneuropathy, whereas less myelotoxic drugs should be preferred in those with compromised bone marrow function. An oral regimen may be preferred in patients living far away from their myeloma treatment center.[68]

In young patients, a second ASCT procedure may be considered, provided the patient responded well to the previous ASCT and had a PFS of more than 12 months at least.[69–71] The chance for an excellent response will increase with the duration of the treatment-free interval. Similarly, in elderly patients, the first-line therapy or, in case of multiple prior treatment lines, even the previous treatment can be repeated, provided it led to a significant tumor response, was well tolerated and PFS lasted for more than 6 months.[72]

Changing the treatment regimen and drug class (if possible) for second or further lines of therapy is recommended in patients with an insufficient response, a rapid relapse and poor tolerance. Treatment should be continued until best possible response, provided tolerance is adequate. Whether continuation of rescue treatment until the next relapse or intolerance or whether

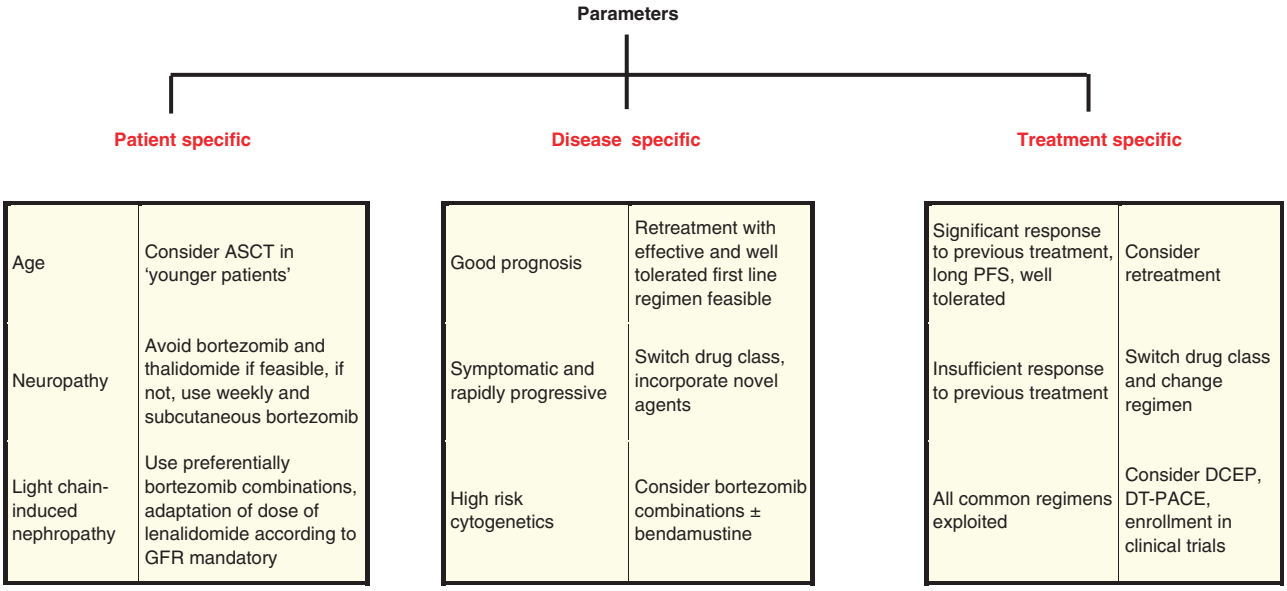

Figure 1. Parameters relevant for treatment selection in patients with relapsed/refractory multiple myeloma.

maintenance therapy will improve outcome is unknown at present. Parameters relevant for treatment selection are shown in Figure 1.

Recently, new effective agents, such as carfilzomib[73] and pomalidomide,[74] have been introduced for the treatment of relapsed/refractory patients, but these drugs are not yet available in several parts of the globe. Patients whose disease has become refractory to novel agents present a particular challenge. They may be enrolled in a clinical trial with novel experimental agents in case this option is available, or may be offered palliative treatment using alkylating agents in combination with corticosteroids, bendamustine-based combinations, high-dose dexamethasone or older regimens, such as the continuous infusion of DCEP or DT-PACE. Allogeneic SCT should, if at all, only be performed in the context of a clinical trial in highly experienced centers and only in patients with good response before transplant, but trials in the relapsed/refractory setting are not available at present.

SUPPORTIVE CARE

Prevention and treatment of bone disease

Bone disease is a hallmark of MM, which may manifest itself as osteoporosis, osteolysis, fractures and, very rarely, osteosclerosis. The substantial loss in bone mass causes devastating complications that result in pain and a reduced quality of life. Bisphosphonates continue to be the mainstay of treatment, as they have demonstrated a reduction in skeletal-related events composed of pathological vertebral fractures, spinal cord compression, hypercalcemia and/or pain requiring surgery, radiotherapy or opioid analgesics.[75] Intravenous zoledronate has been compared with oral clodronate in a large cohort of myeloma patients and was found to supersede clodronate in terms of skeletal-related events and, importantly, also in OS.[76] Pamidronate is another aminobisphosphonate that has been extensively tested in myeloma patients. The usually administered dose is 90 mg every 4 weeks, but a lower dose (30 mg) has been found to be equally effective and better tolerated.[77] The optimal duration of bisphosphonate therapy requires further investigation in trials. Bisphosphonates should be discontinued after 2 years in patients achieving complete response and may be continued in those with active disease or restarted if the patient meets disease progression criteria.[78] Interestingly, the MRC IX trial showed that treatment with bisphosphonates for 2 or more years was associated with a significant improvement in OS compared with clodronate, suggesting that treatment beyond the generally recommended duration of 2 years may be associated with substantial benefits.[79] However, further data are needed. Whether denosumab, a monoclonal antibody against RANKL, will become a therapeutic option in MM depends on the outcome of a currently ongoing large randomized trial evaluating denosumab in comparison with zoledronate.

In addition, patients with bone disease should be monitored for calcium and vitamin D levels and receive calcium and vitamin D supplementation if one of these parameters is low. Local radiotherapy (20-40 Gy) usually results in the rapid improvement of bone pain, and concerns about harming normal bone marrow function are unfounded, provided radiotherapy is focused on localized myeloma lesions only.[80] In patients with a limited number of painful vertebral compression fractures, balloon kyphoplasty or vertebroplasty usually result in immediate pain relief.[81,82] Osteosynthesis or other surgical management of fractures of long bones or of other complications may be required in individual cases. The positive results obtained in patients without overt bone disease at baseline, who were treated with zoledronate, indicate that bisphosphonate therapy should be offered to all patients in need of anti-myeloma chemotherapy. The recommendations for DEXA scanning are those issued for the general population and relate particularly to postmenopausal women.

Prevention of infections

Infections are frequent, and often serious complications in MM that significantly increase morbidity and mortality and should therefore be managed proactively and aggressively.[83–85] Importantly, the risk of infections is highest during the first cycles of therapy and subsequently during episodes of active disease. Because of frequent substantial humoral and cellular immunosuppression, patients are at a higher risk of developing infections involving encapsulated pathogens, such as pneumococci and haemophilus influenzae, as well as viral infections. Although the response to vaccination is frequently impaired in patients with MM,[86] prophylactic vaccination is recommended for influenza A and B virus, pneumococci and haemophilus influenzae. Care givers and patient relatives should

also be vaccinated against influenza, but scientific data supporting this recommendation are scarce. Live vaccines should be avoided because of the risk for vaccine-induced infection due to the compromised immune response in many patients.

In patients receiving bortezomib-containing regimens, the routine use of acyclovir prophylaxis is recommended to prevent herpes zoster infection, which was seen in 13% of patients without prophylaxis in the APEX trial.[87] With acyclovir, the risk can markedly be reduced.[88] Differing results have been published on the efficacy of prophylactic antibiotics.[89,90] The risk of bacterial infections depends on various factors, such as the state of the disease, the type and intensity of therapy and patient-specific immune factors. Patients with a high risk of developing an infection likely benefit from quinolone or trimethoprim-sulfamethoxazole prophylaxis, whereas in other patients prophylaxis may not be helpful. The administration of intravenous immunoglobulins reduced the incidence of infections in patients in the plateau phase, and the effect was most pronounced in those with an impaired response to pneumovax.[91] However, these data were based on a small study. Routine use of fluconazole prophylaxis is not recommended, but there may be exceptions in patients treated with high doses of glucocorticosteroids and in those at a higher risk of mucocutaneous candidiasis. Pneumocystis prophylaxis with trimethoprim–sulfamethoxazole may be considered in patients undergoing stem cell transplantation.

Active infections should be diagnosed immediately, and empiric treatment should be installed as fast as possible, with appropriate treatment adaptions being made when results of blood cultures and other tests become available. It is appropriate that patients keep an emergency supply of ciprofloxacin or amoxicillin and clavulanic acid at home so that they can start antibiotics if instructed on the telephone

Renal failure

Renal failure is a serious complication associated with an increased risk of infections and a shorter survival.[92] It is important to distinguish between non-paraprotein-related causes and pathogenic light-chain-induced renal impairment in order to implement effective interventions. Non-paraprotein-related causes of renal failure include infection, nephrotoxic drugs, hypercalcemia, dehydration, hyperviscosity, myeloma cell infiltration of kidneys and other possible renal pathologies.[93] Renal failure due to pathogenic light chains can manifest itself as cast nephropathy, amyloidosis, light-chain deposit disease or Fanconi syndrome. The prompt management of renal failure with the aim of restoring function is paramount to increase the likelihood of response to treatment and to improve survival.[94]

Once pathogenic light chains have been identified as the cause of renal failure, the following interventions should be initiated immediately: discontinuation of any nephrotoxic medication, adequate hydration and fluid balance. In addition, alkalinization should be considered. Furthermore, an effective myeloma therapy regimen should be chosen to reduce the amount of toxic light chains. Recommended myeloma therapies include thalidomide, lenalidomide and bortezomib, all of which have been shown to be effective in patients with renal impairment; improvements in renal function have been seen with all of these therapies,[94,95] but bortezomib-based regimens seem to be most active.[96] In addition, the use of high-dose dexamethasone[97] during the first treatment cycle is recommended. For thalidomide-based therapy, dose adjustments according to glomerular filtration rate are not required. However, increased episodes of hyperkalemia have been reported and, furthermore, thalidomide-specific toxicities have been observed more frequently in patients with creatinine levels >3.0 mg/dl. With bortezomib-based regimens, dose adjustments according to glomerular filtration rate are not required. It is recommended to use bortezomib at full dose to achieve a rapid response. Recent data show that clearance of carfilzomib is independent of renal function and may also safely be used in patients with renal impairment.[98] With any lenalidomide-based treatment, dose adjustments according to glomerular filtration rate are essential. With regard to mechanical devices for the removal of light chains, the benefit for plasmapheresis has so far not been proven. In addition, the use of special dialysis membranes and long-term dialysis for the removal of serum free light-chains is not yet established. Special care should be taken to prevent infections or, in case of the development of acute infections, to immediately install adequate treatment.

Anemia

Anemia is a frequent complication of myeloma and, depending on the definition of anemia, treatment intensity and patient age, may be found in 40–100% of patients.[99] The pathogenesis of anemia in MM is usually multifactorial, with chronic anemia of cancer and cancer therapy being frequent causes. The consequences of anemia are frequently pronounced in the typically elderly patients with myeloma. Treatment with ESAs should be considered in patients receiving chemotherapy who have hemoglobin levels <10 g/dl. Therapy with either erythropoetin (10 000 U TIW or 40 000 U once weekly) or darbepoetin (150 μg once weekly, or 450 μg q 3 weeks) is recommended. Treatment should be discontinued in case of no response (defined as an increase in Hb of 1.0 g/dl or less) after 6 weeks of treatment. In addition, treatment should be discontinued in case Hb levels increase beyond 12 g/dl. Of note, ASH/ASCO guidelines recommend the discontinuation of treatment already at an Hb level of 10 g/dl.[100] Finally, iv iron supplementation should be considered in case of absolute (TSAT $<20\%$, ferritin <30 μg/L) or functional (TSAT $<20\%$) iron deficiency. It is acknowledged that ESAs are not available in all countries, and concerns regarding increased risk for thromboembolic complications and for mortality when used in nonapproved indications led to restrictive use. Red blood cell transfusions should be used in patients with Hb <8 g/dl who do not respond to erythropoetins or are not candidates for erythropoietin therapy because of their possible risks. Red blood cell transfusions, however, are clearly indicated in patients who are severely symptomatic because of anemia and in need for immediate improvement. Besides the well-known possible complications of RBC transfusions, recent data indicated previously unidentified risks such as higher rate of infections, thromboembolic complications and recurrence of cancer.[101]

Venous thrombolic events (VTEs)

Patients with MM have an increased risk for VTEs,[102] which is further exacerbated by certain patient-specific risk factors and by some of the available myeloma therapies, in particular by thalidomide and lenalidomide treatment. The occurrence of VTEs is associated with shorter survival, and an important goal in the management of patients with MM is therefore the prevention of VTEs.[103]

In an individual patient, possible risk factors, such as obesity, previous VTE, cardiovascular complications or a pacemaker, associated disease (cardiac disease, chronic renal disease, diabetes mellitus, acute infection and immobilization) and surgery (general surgery, any anesthesia and trauma) should be assessed. In addition, the use of IMiDs and of erythropoietin and the presence of blood clotting disorders have to be considered. In the presence of $\leqslant 1$ risk factor, prophylaxis should consist of 81–325 mg aspirin, whereas in the presence of $\geqslant 2$ risk factors LMWH or full-dose warfarin should be administered. For warfarin, the target INR is 2–3. Aside from patient-specific risk factors, full-dose warfarin or LMWH should be considered if thalidomide or lenalidomide are used in

Table 4. Recommendations for dose adaptations in patients with thalidomide- or bortezomib-induced neuropathy

Thalidomide-induced polyneuropathy		Bortezomib-induced polyneuropathy	
Grade	**Intervention**	**Grade**	**Intervention**
1	Reduce thalidomide dose by 50%	1	If patient is on twice-weekly schedule[a]: reduce current bortezomib dose by one level[b] or prolong dosing interval to once-weekly If patient is on once-weekly schedule: reduce bortezomib dose by one level[b]
2	Discontinue thalidomide If neuropathy resolves to grade 1 or better, treatment may be restarted at 50% dose reduction	1 with pain or 2	Same as above, but if patient is already on a once weekly schedule: consider temporary discontinuation or reduction of bortezomib dose by one level[b] If neuropathy resolves to grade 1 without pain or better, once-weekly bortezomib at reduced dose may be restarted
3 and 4	Discontinue thalidomide	2 with pain or 3 or 4	Discontinue bortezomib

[a]Patients ⩾75 years may be immediately started on once-weekly regimen when initiating bortezomib. [b]Bortezomib dose reductions: standard dose, 1.3 mg/m^2; dose reduced by 1 level, 1.0 mg/m^2; dose reduced by 2 levels, 0.7 mg/m^2.

Table 5. Recommended supportive care strategies for myeloma-associated complications

Complication	Intervention
Bone disease	• Bisphosphonates (pamidronate, zoledronate) • Calcium, Vitamin D • Local radiotherapy • Surgical intervention in case of fractures/risk for fractures
Infection	• Vaccination for influenza A and B virus, pneumococci, hemophilus influenza • Prophylactic antibiotics for patients at high risk • Acyclovir for patients receiving bortezomib • Essential to act promptly in case of documented infection
Anemia	• Erythropoetin (10.000 U TIW or 40.000 U once weekly) • Darbepoetin (150μg once weekly, or 450 μg q 3 weeks) • Red blood cell transfusions for patients with severe symptoms and those not responding or who are not candidates for erythropoietin therapy.
Venous thrombolic events	Risk-adapted approach: • ≤ 1 risk factor[a]: aspirin 81-325 mg • ≥ 2 risk factors: LMWH or full-dose warfarin (target INR 2-3) • Full-dose warfarin or LMWH may be indicated for patients receiving thalidomide or lenalidomide in combination with high-dose dexamethasone or doxorubicin
Polyneuropathy	• Close monitoring • Dose and/or schedule adjustments[b]
Pain	• Local radiotherapy or surgical interventions • Analgesics, administered based on the three-step pain ladder developed by the WHO

Abbreviation: LMWH, low-molecular-weight heparin. [a]See text for risk factor assessment. [b]See Table 4.

combination with high-dose dexamethasone, or doxorubicin as part of multi-agent chemotherapy.[104,105]

Polyneuropathy

Polyneuropathy (PNP) can be a dose- or treatment-limiting complication in MM. About 15% of patients present with PNP[106] related to causes other than myeloma therapy, such as diabetes, excessive alcohol consumption, vitamin B12 deficiency or myeloma-related factors and unknown causes. Most frequently, PNP evolves as an untoward side effect of thalidomide and/or bortezomib therapy. Thalidomide primarily induces dorsal root ganglion and axonal damage, whereas dorsal root ganglia and small fibers are predominantly affected by bortezomib therapy.[107] The clinical symptoms also vary. Thalidomide typically induces a dose-dependent sensory, rather than motor, neuropathy, with

numbness, paresthesias and pain. It often develops as a stinging sensation or numbness in the toes or sometimes in the fingers and then spreads along the legs and arms. Genetic variations in certain genes predispose individuals for this drug-associated toxicity.[108] Because nerve electrophysiological studies do not reliably predict PNP,[109] patients need to be assessed carefully and patient self-reporting instruments may be preferable. There is no causative definitive treatment, and therapy of symptoms is only marginally effective. The most important action relies on the early recognition of evolving PNP and dose reduction or treatment discontinuation, as there is only little improvement in symptoms when PNP is established.[110]

Bortezomib therapy frequently results in a distal sensory PNP, which may be painful, particularly at higher grades.[110] Newer studies suggest an important role for the patient-specific genetic background in conferring increased susceptibility to bortezomib-induced PNP (BiPNP).[110,111] Recommendations for dose reductions in patients experiencing neuropathic toxicity during thalidomide or bortezomib therapy are shown in Table 4. The suggestions for BiPNP have been developed for the intravenous administration of bortezomib. At the current time, they should also be applied to patients receiving bortezomib via subcutaneous injection, which is less frequently associated with BiPN.[112] After the discontinuation of bortezomib, BiPN usually improves in most patients, although complete resolution is seen in only a minority.

Pain

The first step in the management of pain should be to ascertain its origin, its quality and intensity to enable the initiation of effective relief aimed at the particular cause, character and grade. Recommended treatments for pain include local radiotherapy or surgical interventions in addition to analgesics, which should be administered on the basis of the three-step pain ladder developed by the WHO (http://www.who.int/cancer/palliative/painladder/en/). Nonsteroidal anti-inflammatory drugs are quite effective at ameliorating the pain due to myeloma-induced bone disease, but should be administered with care, as one of their possible side effects is the reduction in glomerular perfusion, which might aggravate or lead to renal impairment. Whenever possible, the oral or transcutaneous route should be chosen preferentially over the parenteral route. It can be helpful to use visual analog or categorical scales for the patient self-assessment of pain. It is important to be prepared to manage breakthrough pain preferably by administering fentanyl via mucosal absorption or by iv injection.[113] Concerning neuropathic pain, antidepressants and anticonvulsants (gabapentin, pregabalin) have a specific role. Finally, appropriate co-medication, such as laxatives, anti-emetics at the start of opioid therapy, corticosteroids and anti-depressants for depression should form part of the pain management strategy. Recommended supportive care strategies for myeloma-associated complications are summarized in Table 5.

CONCLUSIONS

Establishing the diagnosis of MM, the assessment of stage, the initiation of the appropriate treatment and the monitoring of its effects, as well as the management of the side effects of therapy and the symptoms of the disease, require professional competence, experience and commitment to optimal patient care. This overview provides the theoretical backbone for the manifold considerations and decisions that are required to cover the medical needs of patients affected by MM and to select the best possible strategy given the variations in availability of novel procedures and drugs. It is hoped that it will support interested readers in optimizing their clinical care of patients with MM.

CONFLICT OF INTEREST

Heinz Ludwig received honoraria and research funding from Celgene, Janssen-Cilag and Mundipharma; Jesus San Miguel received honoraria from Celgene, Millenium and Janssen-Cilag; Meltios Dimopoulos received honoraria from Celgene and Novartis; Antonio Palumbo received honoraria from Celgene, Janssen-Cilag and Millenium; Ramon Garcia Sanz received honoraria from Ortho-Biotech and Celgene; Suzanne Lentsch received honoraria and research funding from Celgene; Jian Hou received honoraria from Novartis and is member of the steering committee of Novartis; Roman Hajek received honoraria from Merck and Celgene; Evangelos Terpos received honoraria from Celgene; Kazuyuki Shimizu received honoraria from Celgene; Douglas Joshua received honoraria from Celgene and Janssen-Cilag for speakers forum and advisory board functions; Elena Zamagni received honoraria from Janssen-Cilag and Celgene; and Brian Durie received research funding and honoraria from Celgene, Merck, Millenium and Novartis. Raymond Powles, Wen Ming Chen, Artur Jurczynszyn, Kenneth Romeril, Vania Hungria, Angelina Rodrigues Morales, Dina Ben-Yehuda and Pia Sondergeld did not declare any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors participated actively in the IMWG summit in Amsterdam and contributed to the workshop on global myeloma care. The outcome of the meeting was summarized in an initial draft, which was circulated, modified and/or commented by all authors. All authors contributed to the manuscript. Heinz Ludwig and Pia Sondergeld served as writers.

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