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Multiple myeloma – 2020 update on diagnosis and management

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There has been remarkable progress made in the diagnosis and treatment of multiple myeloma (MM). The median survival of the disease has doubled as a result of several new active drugs. These advances have necessitated a revision of the disease definition and staging of MM. Until recently, MM was defined by the presence of end-organ damage, specifically hypercalcemia, renal failure, anaemia, and bone lesions (CRAB features) that can be attributed to the clonal process. In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MM to add three specific biomarkers that can be used to diagnose the disease in patients who did not have CRAB features: clonal bone marrow plasma cells greater than or equal to 60%, serum free light chain (FLC) ratio greater than or equal to 100 provided involved FLC level is 100 mg/l or higher, or more than one focal lesion on MRI. In addition, the definition was revised to allow CT and PET-CT to diagnose MM bone disease.

With the introduction of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs), major improvements have been achieved in the treatment and outcome of MM. Different treatment combinations are now in use and newer therapies are being developed. However, nearly all MM patients ultimately relapse, even those who experience a complete response to initial therapy. Management of the relapsed disease remains a critical aspect of MM care and an important area of ongoing research. The aim of this review is to summarise the current methods of diagnosis and treatment of MM.

Key words: multiple myeloma, diagnosis, treatment, novel agents, transplantation, supportive care

Incidence and epidemiology

Multiple myeloma (MM) accounts for 1% of all cancers and 10-15% of all blood cancers. The incidence in Europe is 4.5–6.0/100 000/year with a median age at diagnosis of 72 years; the mortality is 4.1/100 000/year [1]. Over 90% of MM cases refer to patients >50 years old. Only 35% of the patients are younger than 65 years at the moment of diagnosis. Individuals under 40 years of age count for up to 2% of all cases [2]. The annual incidence in Poland in 2017 was approximately 8/100 000/year [3]. The median overall survival in MM is approximately 6 years [4]. In the subset of patients eligible for autologous stem cell transplantation (ASCT), 4-year survival rates are more than 80%; the median overall survival (OS) among these patients is approximately 8 years [5]. Among elderly patients (age >75 years), median OS is lower, and is approximately 5 years [4]. Particularly poor prognosis concerns MM patients with central nervous system involvement (median OS: 7 month) [6].

Multiple myeloma arises from a terminally differentiated postgerminal centre plasma cell. The pathogenesis of MM is complex, and many steps in the pathway are not fully elucidated. Most cases of MM are preceded by the premalignant asymptomatic states of monoclonal gammopathy of undetermined significance (MGUS) and smouldering MM (SMM) [7]. The progression of MGUS to MM is approximately 1% of cases

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per year, whereas SMM has a much higher rate of progression of 10% of cases annually. Approximately 73% of SMM patients will progress to MM within 15 years [8].

Multiple myeloma is a heterogeneous disease that is based on various genetic aberrations. Many of the chromosomal abnormalities include translocations in the immunoglobulin--heavy chain of chromosome 14, aberrations in chromosomes 1, 5, 13, and 17, and trisomies [9]. Genetic abnormalities and molecular changes are thought to contribute to cell-cycle dysregulation and lead to active MM [10].

Diagnosis

In 2014, the International Myeloma Working Group (IMWG) revised the diagnostic criteria for MM [10]. The revised diagnostic criteria for MM allow the use of specific biomarkers to define the disease in addition to the established CRAB (hyperCalcaemia, Renal failure, Anaemia, or lytic Bone lesions) features. They also allow the use of modern imaging tools to diagnose MM bone disease and clarify several other diagnostic requirements.

The diagnosis of MM requires the presence of one or more MM defining events in addition to evidence of either 10% or more clonal plasma cells (PC) in bone marrow (BM) examination or a biopsy-proven plasmacytoma. Multiple myeloma defining events consists of established CRAB features as well as three specific biomarkers: clonal PC in BM ≥60%, serum free light chain (sFLC) ratio ≥100 (provided involved FLC level is ≥100 mg/l), and more than one focal lesion on magnetic resonance imaging (MRI). Diagnosis of MM should be based on the following tests [11, 12]:

1. Detection and evaluation of the monoclonal (M) component by serum and/or urine protein electrophoresis (concentrate of 24 hours urine collection); nephelometric quantification of IgG, IgA and IgM immunoglobulins; characterisation of the heavy and light chains by immunofixation; and serum FLC measurement.
2. Evaluation of BM, PC infiltration: BM aspiration and/or biopsy. Moreover, the BM sample should be used for cytogenetic/fluorescent *in situ* hybridisation (FISH) studies on immunologically recognised or sorted PC and also has the potential for immunophenotypic and molecular investigations.
3. Evaluation of lytic bone lesions: whole-body low-dose computed tomography (WBLD-CT) is the new standard for the diagnosis of lytic disease. Conventional radiography can also be used if WBLD-CT is not available. 18F-fluorodeoxyglucose positron emission tomography with CT (PET--CT) can be performed to evaluate bone lesions, according to availability and resources.
4. Complete blood cell count, with differential serum creatinine, creatinine clearance and calcium level.

The definition of MGUS has not changed. Patients need to have less than 30 g/l serum M-protein, less than 10% clonal PC in BM, and no end-organ damage for this diagnosis. Currently no data is available to support the treatment of MGUS patients.

The diagnosis of a MM demands the presence of a serum M-protein of ≥30 g/l, and/or ≥10% of clonal PC in BM. Asymptomatic patients without myeloma-defining events have a so-called SMM, which may progress to a symptomatic MM over time. The presence of end organ damage, primarily the CRAB--criteria, define an underlying MM in need of therapy. In the most recent update of the criteria for diagnosis of MM, three additional myeloma-defining events have been introduced to discriminate symptomatic MM without evidence of classical end-organ damage from SMM: clonal PC of 60% or greater in the bone marrow, a serum FLC ratio of 100 or greater, or more than one focal lesion larger than 5 mm on MRI [10]. To address these additional MM defining events, the term "SLiM-CRAB" (SLiM: S = sixty; Li = light chain; M = MRI) was coined soon after publication of the updated criteria. The new definitions of MGUS, SMM and symptomatic MM are shown in table I [10].

Staging and risk classification

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 ß2-microglobulin, albumin, C-reactive protein (CRP), and lactate dehydrogenase (LDH). More precise estimation of prognosis requires an assessment of multiple factors. As in other cancers, OS in MM is affected by host characteristics, tumour burden (stage), biology (cytogenetic abnormalities), and response to therapy [13].

Tumour burden in MM has traditionally been assessed using the Durie-Salmon Staging (DSS). The International Staging System (ISS) has now replaced the DSS system [14]. The R-ISS staging system is a new risk stratification algorithm with an improved prognostic power incorporating ISS, chromosomal abnormalities, and LDH levels (tab. II) [15].

Some institutions are also incorporating a risk-adapted approach to treatment decisions. The Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) classifies risk based on cytogenetic abnormalities [16]. Patients with deletions of the long arm of chromosome 13 and translocations of chromosomes 4 and 14 are considered to have high-risk disease. Deletion of 17p13, which results in mutations in the tumour-suppressor protein 53, is also associated with a poorer outcome [16].

Response evaluation

The definition of response established by the IMWG in 2006 has been updated in 2016 [17]. The IMWG uniform response criteria are most often used to assess response to drug therapy. Responses include stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), and stable disease (SD) [17]. The response criteria incorporate the degree of reduction of serum, and urine M-protein by electrophoresis and immunofixation, plasmacy-

Table I. Diagnostic criteria for monoclonal gammopathy of undetermined significance, smouldering multiple myeloma, and symptomatic multiple myeloma

Definition of Monoclonal gammopathy of undetermined significance
All tree criteria must be met: • serum M-protein (non-IgM type) <30 g/l • clonal bone marrow plasma cells <10%* • absence of end-organ damage such as hyperCalcemia, renal insufficiency, anaemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Definition of smouldering multiple myeloma
Both criteria must be met: • serum M-protein (IgG or IgA) ≥30 g/l, or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10–60% • absence of MM defining events or amyloidosis
Definition of symptomatic multiple myeloma
Both criteria must be met: • Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma • Any one or more of the following MM defining events: – Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: · Hypercalcemia: serum Ca >0.25 mmol/l (>1 mg/dl) higher than the upper limit of normal or >2.75 mmol/l (> 11 mg/dl), · Renal insufficiency: CrCl <40 ml per minute or serum creatinine >177 µmol/l (>2 mg/dl), · Anaemia: Hb value of >2 g/dl below the lower limit of normal, or a Hb value <10 g/dl, · Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT – Clonal bone marrow plasma cell percentage ≥60% – Involved: uninvolved serum FLC ratio ≥100 (involved FLC level must be ≥100 mg/l) – >1 focal lesions on MRI studies (at least 5 mm in size)

Ca – calcium; CT – computed tomography; CrCl – creatinine clearance; FLC – free light chain; Hb – hemoglobin; Ig – immunoglobuline; MRI – magnetic resonance imaging; MM – multiple myeloma; PET-CT – positron emission tomography-CT

*A bone marrow can be deferred in patients with low risk MGUS (IgG type, M protein <15 g/l, normal free light chain ratio) in whom there are no clinical features concerning for myeloma

Table II. The International staging system (ISS) and revised International staging system (R-ISS) for multiple myeloma

Stage	Criteria	Frequency (%)	Median OS (months)
	ISS		
I	• β2-microglobulin <3.5 mg/l, and • Albumin (serum) ≥35 g/l	28	62
II	• Neither I or III	62	45
III	• β2-microglobulin ≥5.5 mg/l	10	29
	R-ISS		
I	• β2-microglobulin <3.5 mg/l, • Albumin (serum) ≥35 g/l, and • No high-risk cytogenetics, and • Normal LDH (defined as less than ULN)	28	82
II	• Not R-ISS stage I or III	62	62
III	• β2-microglobulin ≥5.5 mg/l regardless of albumin levels (serum), and • High-risk cytogenetics: del(17p), t (4;14) or t (14;16) or • High LDH (defined as higher than ULN)	10	40

ISS – International staging system; LDH – lactate dehydrogenase; OS – overall survival; R-ISS – revised International staging system; ULN – upper limit of normal

tomas, and PC in BM. Standard IMWG uniform response criteria for MM are presented in table III [17].

The quality and the depth of response have improved over the last 5 years in the context of novel agent-based therapies, allowing for the introduction of new response grades, namely minimal residual disease (MRD) criteria including sequencing MRD negativity, flow MRD negativity, imaging plus negativity and sustained MRD negativity. There is a statistical relationship between the achievement of CR, MRD negativity and progression free survival (PFS), or OS.

Treatment overview

The goals of MM treatment have evolved with advances in drug therapy, and more sensitive monitoring. The primary goal is to achieve a deep, long-lasting response. Additionally, therapy should control disease, minimise complications, and improve quality of life. Myeloma treatment depends on whether the patient is symptomatic. Patients with MGUS, and SMM are usually observed, and treatment is initiated upon disease progression to active MM. There is no evidence that early treatment of SMM prolongs OS. Patients with symptomatic

Table III. Standard International Myeloma Working Group uniform response criteria for multiple myeloma

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 multiparametric flow cytometry (with >4 colours)
Stringent CR	CR as defined below plus normal sFLC ratio and absence of clonal PCs in BM biopsy by immunohistochemistry or 2- to 4-colour flow cytometry
CR	Negative IF 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 IF but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours
PR	• ≥50% reduction of serum M-protein plus reduction in 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hours. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required. • If serum and urine M-protein are unmeasurable, and sFLC assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow PCs percentage was ≥30%. • In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50–89%. • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
PD	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: – Serum M-protein (absolute increase must be ≥5 g/l), – Serum M-protein increase ≥10 g/l, if the lowest M component was ≥5 g/dl,\ – Urine M-protein (absolute increase must be ≥ 200 mg/24 hours). • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved sFLC levels (absolute increase must be >10 mg/dl). • In patients without measurable serum and urine M-protein levels and without measurable involved sFLC levels, BM PCs percentage irrespective of baseline status (absolute increase must be ≥10%). • Appearance of (a) new lesion(s), ≥50% increase from nadir of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis, ≥50% increase in circulating PCs (minimum of 200 cells per µl) if this is the only measure of disease.

ASO-PCR – allele-specific oligonucleotide polymerase chain reaction; BM – bone marrow; CR – complete response; IF – immunofixation; M – monoclonal; MR – minimal response; PR – partial response; PCs – plasma cells; PD – progression disease; sFLC – serum free light chain; VGPR – very good partial response

MM require treatment. This treatment is patient-specific and depends on numerous factors, including cytogenetics, disease stage, age, comorbidities, and performance status.

Survival in MM has improved significantly in the last 15 year. The initial impact came from the introduction of thalidomide, bortezomib, and lenalidomide. In the last decade, carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, daratumumab, isatuximab, and selinexor have been approved by the European Medicines Agency (EMA) for the treatment of relapsed MM, and promise to improve outcomes further.

All patients with a diagnosis of symptomatic MM require immediate treatment. Initial choice of therapy is driven by whether a patient is eligible for an ASCT, because certain agents, such as alkylating agents, should typically be avoided in those who are transplant eligible. Initial therapy for patients with MM is also based on genetic risk stratification of the disease. Patients with high-risk disease require a CR treatment for long-term OS and thus benefit from an aggressive treatment strategy. Standard-risk patients have similar OS regardless of whether or not CR is achieved and thus can either be treated with an aggressive approach, or a sequential therapy approach.

The clinician must decide whether the patient is eligible or not for ASCT. The eligibility criteria vary from country to country. In European countries, ASCT is recommended under 65–70 years of age, but nowadays it depends upon the "physiological age" rather than the chronological age of the patient. Furthermore, serum creatinine level, the Eastern Cooperation Oncology Group (ECOG) performance status, and the New York Heart Association functional status need to be considered. The current guidance of European Society for Medical Oncology (ESMO) for MM treatment is shown in figure 1 [18].

Initial treatment in patients eligible for autologous stem cell transplantation

The current treatment paradigm for newly diagnosed MM patient eligible for ASCT consists of four phases: induction remission, transplantation, post-transplant treatment (consolidation, and maintenance therapy).

Induction remission

Induction therapy usually consists of four to six cycles of therapy with the aim of achieving rapid disease control, improving symptoms and allowing for subsequent stem cell collection. Bortezomib with dexamethasone (VD) is the standard back-

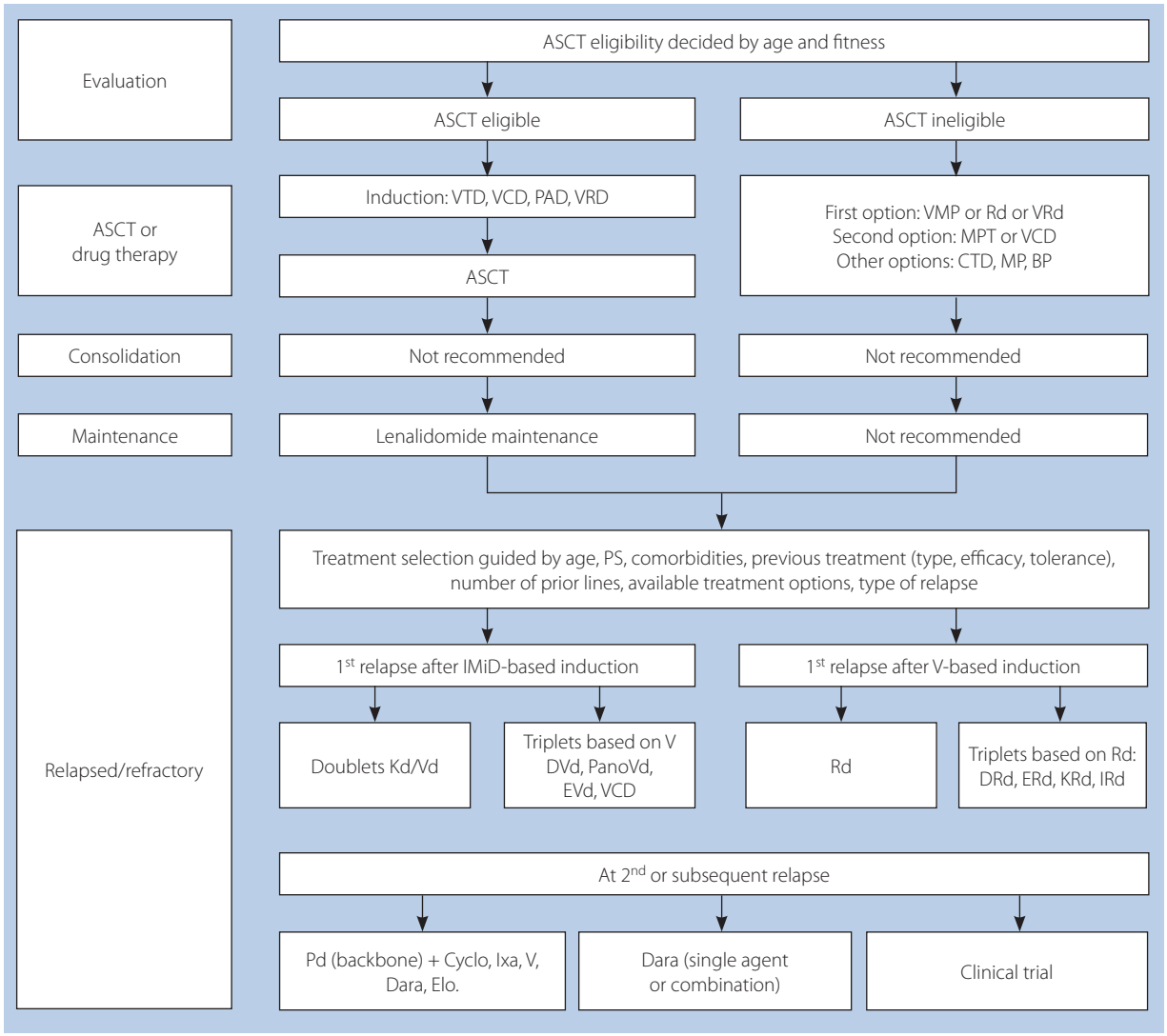

Figure 1. European Society for Medical Oncology guidance for multiple myeloma treatment; ASCT – autologous stem cell transplantation; BP – bendamustine, prednisone; Cyclo – cyclophosphamide; CTD – cyclophosphamide, thalidomide, dexamethasone; Dara – daratumumab; DVd – daratumumab, bortezomib, dexamethasone; Elo – elotuzumab; ERd – elotuzumab, lenalidomide, dexamethasone; EVd – elotuzumab, bortezomib, dexamethasone; Ixa – ixazomib; IRd – ixazomib, lenalidomide, dexamethasone; IMiD – immunomodulathory drug; Kd – karfilzomib, dexamethasone; MP – melphalan, prednisone; MPT – melphalan, prednisone, thalidomide; PAD – bortezomib, doxorubicin, dexamethasone; PanoVd – panobinostat, bortezomib, dexamethasone; Pd – pomalidomide, dexamethasone; PS – personal status; Rd – lenalidomide, low-dose dexamethasone; RVD – lenalidomide, bortezomib, dexamethasone; V – bortezomib; VCD – bortezomib, cyclophosphamide, dexamethasone; Vd – bortezomib, dexamethasone; VMP – bortezomib, melphalan, prednisone; VRd – bortezomib, lenalidomide, low-dose dexamethasone; VTD – bortezomib, thalidomide, dexamethasone

bone of induction therapy [19, 20]. The addition of a third agent, thalidomide (VTD) [21], cyclophosphamide (VCD) [22], doxorubicine (PAD) [23], or lenalidomide (VRD) [24] provides higher response rates. In prospective trials, induction with VTD is superior to VCD in terms of response rate, at the cost of a higher incidence of peripheral polyneuropathy (PN) but lower incidence of haematological toxicities [25]. To reduce the PN incidence, the French Intergroupe Francophone du Myelome (IFM) proposed the VTD regimen with reduced doses of bortezomib, and thalidomide, which is associated with a lower incidence grade ¾ PN (14% *vs.* 34%), but at the expense of lower response rates [26]. Bortezomib, cyclophosphamide, and dexamethasone was also shown to be, as effective as PAD in terms of response, but less toxic [27]. Replacement of thalidomide by lenalidomide in the VRD regimen induces higher CR rates before and after ASCT (47%, and 88% of patients with a VGPR or better, respectively) [24]. Current regimens used in the front-line are listed in table IV.

Other highly effective combinations such as carfilzomib, lenalidomide, and dexamethasone (KRd), or ixazomib, lenalidomide, and dexamethasone (IRd) are currently under evaluation in phase III trials.

However, the introduction of monoclonal antibodies will change the landscape of induction therapy in the near future. Ongoing prospective trials combining daratumumab with VTD (Cassiopeia) or VRD (Perseus), or elotuzumab with VRD are exploring the role of induction with antibody-based quadruplets.

Stem cell collection

Peripheral blood progenitor cells are usually collected for more than one ASCT (at least 2.5 x 10^6 CD34 + cells/kg per transplantation). Since the use of lenalidomide can impair stem cell collection, apheresis in this situation should be performed after 3–4 cycles, and may require the use of cyclophosphamide or plerixafor.

High dose melphalan (HDM) and ASCT

High-dose melphalan (melphalan 200 mg/m^2, MEL200) remains the standard conditioning regimen prior to ASCT. A dose reduction (100–140 mg/m^2) is recommended in case of renal impairment (estimated GFR <60 ml/min). In this group of patients, including those requiring dialysis, ASCT is feasible but exposes the patient to severe mucositis, prolonged hospitalisation and an increased risk of transplant-related mortality (4% *vs.* <1%) [28].

Post-transplant treatment

The concept of consolidation and/or maintenance is a commonly adopted approach after transplantation. Consolidation after ASCT is a short-term intensive therapy aimed at improving the quality of response after transplant. Maintenance consists of the administration of a therapy for a prolonged period in order to maintain the response achieved after ASCT and prevent progression.

Consolidation with second ASCT

Before the era of novel agents, the main approach was to propose a second ASCT. However, tandem ASCT did not provide any OS, or PFS advantage, except in patients not achieving VGPR after the first transplant. [29, 30]. Currently, tandem ASCT with HDM as conditioning is recommended for transplant-eligible patients with high-risk cytogenetic features at diagnosis.

Consolidation with new drugs

Initially, bortezomib or VT(D) consolidation were shown to increase the quality of response by 30% and were considered at least in patients who failed to achieve a VGPR or CR/near CR (nCR) after ASCT [31] Nowadays, the role of consolidation remains unclear. Trials using either carfilzomib or ixazomib in this setting are currently ongoing. Overall, consolidation remains a reasonable practice in patients who failed to achieve a VGPR or nCR/CR after transplantation.

Maintenance therapy

In young patients following ASCT, phase III randomised trials have demonstrated that maintenance therapy with immunomodulatory drugs (IMiDs), either thalidomide or lenalidomide, prolongs PFS [19]. A meta-analysis demonstrated that lenalidomide maintenance following ASCT is associated with an overall OS benefit of more than two years [32]. Bortezomib maintenance was also evaluated during a two-year study and was associated with a survival benefit over thalidomide maintenance, but induction was not identical in the two arms of this prospective trial [23]. Currently, bortezomib and thalidomide are not approved in this setting.

In elderly patients following induction, several randomised trials have explored the benefit of maintenance therapy in terms of OS using either IMiDs or bortezomib: melphalan with prednisone (MP) or a reduced-dose regimen of cyclophosphamide, thalidomide, and dexamethasone (CTD) with or without thalidomide maintenance [33], MP versus melphalan, prednisone, lenalidomide (MPR) versus melphalan, prednisone, lenalidomide and followed by maintenance with lenalidomide (MPR-R) [34], bortezomib, melphalan, prednisone, thalidomide followed by maintenance with bortezomib, and thalidomide (VMPT-VT) versus bortezomib, melphalan, prednisone (VMP) [35], VMP versus bortezomib, thalidomide, prednisone (VTP) followed by either bortezomib, and prednisone (VP) or VT maintenance [36] systematic maintenance therapy currently can not be recommended in elderly patients.

Initial treatment in patients not eligible for ASCT

For patients with newly-diagnosed (ND) MM who are ineligible for ASCT due to age or other comorbidities, chemotherapy is the only option. Many patients will benefit not only in survival, but also in quality of life. Immunomodulatory agents, such as lenalidomide and thalidomide, and proteasome inhibitors (PIs), such as bortezomib, are highly effective and well tolerated. There has been a general shift to using these agents upfront in transplant-ineligible patients.

All the previously mentioned regimens can also be used in transplant-ineligible patients. Although no longer the preferred treatment, melphalan can be considered in resource--poor settings [37]. Patients who are not transplant-eligible are treated for a fixed period of 9 to 18 months, although lenalidomide, and dexamethasone (Rd) is often continued until relapse [38, 39].

The two following options are recommended based on data from randomised phase III trials: VMP (bortezomib administered subcutaneously) [39] or Rd [40]; both VMP and Rd are approved in this setting by the European Medicines Agency (EMA). Melphalan, prednisone, thalidomide (MPT) is also approved by the EMA, but is inferior to Rd in terms of PFS and OS [40, 41]. The regimen has a high toxicity rate (>50%) and a deep vein thrombosis rate of 20%, so patients undergoing treatment with this regimen require thromboprophylaxis. Bortezomib, cyclophosphamide with dexamethasone induces high response rates and prolonged PFS [19]. Lenalidomide with dexamethasone has recently been compared prospectively with Rd with bortezomib (VRd), and the addition of bortezomib resulted in significantly improved PFS and OS and had an acceptable risk-benefit profile [42]. Bendamustine, and prednisone (BP) is also approved by the EMA in patients who have clinical neuropathy at time of diagnosis, precluding the use

Table IV. Currently used first-line regimens in eligible- and ineligible-transplant newly diagnosed multiple myeloma patients

Regimen	ORR (%)	>VGPR (%)	Median PFS (months)	3-years OS rate (%)
Transplant-eligible				
VTD [21]	93	63	NR	90
VCD [22]	88	71	NA	NA
PAD [23]	90	42	35	61
VRD [24]		CR: 49	50	81% at 4 years
Transplant-ineligible				
MPT [40]	62	28	21.2	51% at 4 years
VMP [39]	71	CR: 30	22	41
Once-weekly VMP [46]	85	55	33.1	88
VCD [22]	88	71	NA	NA
Rd [38] (continuous)	75	44	25.5	59% at 4 years
VRd [42]	81.5	27.8	43	median OS: 75 months

CR – complete response; MPT – melphalan, prednisone, thalidomide; NA – not available; NR – not reached; ORR – overall response rate; OS – overall survival; PAD – bortezomib, doxorubicin, dexamethasone; PFS – progression free survival; Rd – lenalidomide, low-des dexamethasone; VCD – bortezomib, cyclophosphamide, dexamethasone; VGPR – very good partial response; VMP – bortezomib, melphalan, prednisone; VRd – bortezomib, lenalidomide, low-dose dexamethasone; VRD – bortezomib, lenalidomide, dexamethasone; VTD – bortezomib, thalidomide, dexamethasone

Table V. Definitions of relapsed and refractory multiple myeloma

Multiple myeloma	Definition
Primary refractory	Non-responsive disease, in which MR or better has never been achieved, with no significant change in M-protein level, and no evidence of clinical progression
Refractory	Non-responsive disease, while on primary or salvage therapy, or progressing within 60 days of last therapy
Relapsed	Previously responding disease that progresses and requires initiation of salvage therapy, but does not meet criteria for either primary refractory disease or relapsed and refractory disease
Relapsed and refractory	Non responsive disease, while on salvage therapy or progressing within 60 days of last therapy, in patients who have achieved at least MR at some point previously before, then progressing in their course
Double refractory	Disease refractory to both PIs and IMiDs

IMiDs – immunomodulatory inhibitors; MR – minimal response; PI – proteasome inhibitors

of thalidomide according to the MPT regimen or bortezomib according to the VMP regimen [43]. Melphalan, prednisone, and lenalidomide is not routinely used and cannot be considered as a standard of care. Cyclophosphamide, thalidomide, and dexamethasone has also been compared with MP and is superior in terms of response rates, but does not induce a clear survival advantage over MP. Current regimens used in front-line are listed in table IV.

Treatment of relapsed/refractory multiple myeloma

Table V shows definitions of relapsed and refractory (RR) MM [44]. In the relapsed setting, optimal management of MM is complex and ESMO guidelines indicate that the selection of therapy should be guided by a number of different parameters including: patient age; performance status; comorbidities; the type, efficacy and tolerance of the previous treatment; the number of prior treatment lines; the available remaining treatment options; the interval since the last therapy; and the type of relapse [18]. Relapses in MM may be clinical or biochemical, and in the case of biochemical relapse, salvage treatment can be delayed. For the youngest, fittest patients who have initially benefited from their first ASCT, a second ASCT may be considered, although, this option is still infrequently used [18, 45].

For most patients, the treatment approach will need to be based on prior exposure and toxicity. Wherever prior treatment was IMiD-based, current guidelines advise a switch to a proteasome inhibitor (PI) doublet (bortezomib or carfilzomib with dexamethasone) or bortezomib-based triplet therapy with dexamethasone and either daratumumab, panobinostat, elotuzumab or cyclophosphamide (fig. 1) [18].

In first relapse after bortezomib-based induction, treatment should be changed to an IMiD-based treatment regimen with or without a novel agent. Other options include doublet Rd therapy or triplets on an Rd backbone – for example, with the addition of daratumumab, carfilzomib, ixazomib or elotuzumab (fig. 1) [18].

If both IMiD's and PI's have been exhausted and the patient is experiencing a second or subsequent relapse, current ESMO guidelines recommend the alternative option of a clinical trial or daratumumab monotherapy if this has not been previously

tried, while combinations based on a pomalidomide backbone with ixazomib, cyclophosphamide, bortezomib, daratumumab or elotuzumab should also be evaluated (fig. 1) [18].

Compelling data from randomised, controlled phase III trials support the ability of novel agent-based triplets to achieve both superior response rates and prolonged disease control versus doublet combinations. In several phase III studies Rd with ixazomib, carfilzomib, elotuzumab and daratumumab versus Rd alone in patients with RRMM have demonstrated statistically significant improvement in the primary clinical endpoint of PFS when combined with Rd versus Rd alone in patients with RRMM. Table VI shows the results of selected phase III clinical trials assessing IMiD-based (lenalidomide, pomalidomide) chemotherapy in RRMM. Significant improvements in PFS were also obtained with daratumumab or panobinostat when added to a Vd backbone compared to Vd in the relapsed/refractory setting in phase III studies. However, the clinical benefit of triplets may

Table VI. Results of selected phase III clinical trials assessing IMiD-based (lenalidomide, pomalidomide) chemotherapy in relapsed/refractory multiple myeloma

Trial	Regimen	ORR (%)	>CR (%)	Median PFS (months)	Median OS (months)
Lenalidomide-based					
MM-010 [47]	Rd *vs.* Dex	60 *vs.* 24 p < 0.001	16 *vs.* 3.4 p < 0.001	11.3 *vs.* 4.7 p < 0.001 HR = 0.66	NR *vs.* 20.6 p = 0.03 HR = 0.66
ASPIRE [48, 49]	KRd *vs.* Rd	87 *vs.* 67 p < 0.001	32 *vs.* 9 p < 0.001	26 *vs.* 17.6 p = 0.0001 HR = 0.69	2-years: 73% *vs.* 65% p = 0.04 HR = 0.79
TOURMALINE-MM1 [50]	IRd *vs.* Rd	78 *vs.* 71.5 p = 0.004	≥ VGPR: 48 *vs.* 39 p = 0.01	20.6 *vs.* 14.7 p = 0.01 HR = 0.74	NR
POLLUX [51]	DRd *vs.* Rd	93 *vs.* 76.4 p < 0.0001	51 *vs.* 21 p < 0.0001	NR *vs.* 17.5 p < 0.0001 HR = 0.41	NR HR = 0.64
ELOQUENT-2 [52]	ERd *vs.* Rd	79 *vs.* 66 p < 0.001	≥VGPR: 35 *vs.* 29	18.5 *vs.* 14.4 p = 0.0004 HR = 0.72	43.7 *vs.* 39.6 p = 0.0257 HR = 0.77
Pomalidomide-based					
MM-003 [53]	Pd *vs.* Dex	32 *vs.* 11 p < 0.001	7 *vs.* 1	4.0 *vs.* 1.9 p < 0.001 HR = 0.5	13.1 *vs.* 8.1 p = 0.009 HR = 0.72
OPTIMISMM [54]	VPd *vs.* Vd	82 *vs.* 50 p < 0.0001	52.7 *vs.* 18.3 p < 0.0001	11.2 *vs.* 7.1 p < 0.0001 HR = 0.61	NR
ELOQUENT-3 [55]	EPd *vs.* Pd	53 *vs.* 26	20 *vs.* 9	10.3 *vs.* 4.7 p = 0.008 HR = 0.54	NR HR = 0.62

CR – complete response; DRd – daratumumab, lenalidomide, dexamethasone; Dex – dexamethasone; EPd – elotuzumab, pomalidomide, dexamethasone; ERd – elotuzumab, lenalidomide, dexamethasone; HR – hazard ratio; IRd – ixazomib, lenalidomide, dexamethasone; IMiD – immunomodulathory drug; KRd – karfilzomib, lenalidomide, dexamethasone; NR – not reached; ORR – overall response rate; OS – overall survival; Pd – pomalidomide, dexamethasone; PFS – progression free survival; Rd – lenalidomide, dexamethasone; Vd – bortezomib, dexamethasone; VPd – bortezomib, pomalidomide, dexamethasone;

Table VII. Results of selected phase III clinical trials assessing inhibitor proteasoms-based chemotherapy in relapsed/refractory multiple myeloma

Trial	Regimen	ORR (%)	>CR (%)	Median PFS (months)	Median OS (months)
APEX [56]	V *vs.* Dex	38 *vs.* 18 p < 0.001	6 *vs.* 1 p < 0.001	6.2 *vs.* 3.5 p < 0.001 HR = 0.55	12 months: 80% *vs.* 66% p = 0.001 HR = 0.57
ENDEAVOR [57, 58]	Kd *vs.* Vd	77 *vs.* 63 p < 0.0001	13 *vs.* 6 p = 0.001	18.7 *vs.* 9.4 p < 0.0001 HR = 0.53	47.6 *vs.* 40 p = 0.01 HR = 0.79
CASTOR [59]	DVd *vs.* Vd	83.8 *vs.* 63 p < 0.0001	28.8 *vs.* 9.8 p < 0.0001	16.7 *vs.* 7.1 p < 0.0001 HR = 0.31	NR
Panorama-1 [60]	PanoVd *vs.* d	61 *vs.* 57 p = 0.009	28 *vs.* 16	12.0 *vs.* 8.1 p < 0.0001 HR = 0.63	40.3 *vs.* 35.8 p = 0.54 HR = 0.94

Dex – dexamethasone; DVd – daratumumad, bortezomib, dexamethasone; HR – hazard ratio; Kd – karfilzomib, dexamethasone; ORR – overall response rate; OS – overall survival; PanoVd – panobinostat, bortezomib, dexamethasone; PFS – progression free survival; V – bortezomib; Vd – bortezomib, dexamethasone

be less evident in elderly or frail patients. The older or more unfit patients with poor performance status may benefit from less-intensive triplet regimens or dose reductions. Table VII shows the results of selected phase III clinical trials assessing IP-based chemotherapy in RRMM.

Treatment of patients with RRMM in Poland using new drugs (lenalidomide, pomalidomide, daratumumab, carfilzomib) is carried out in accordance with the Ministry of Health's drug programme "Treatment of patients with refractory or recurrent myeloma" which is available at the internet address www.gov.pl/web/zdrowie/zdrowie-onkologiczne [61].

Supportive care

Patients with RRMM are more at risk of frequent infections, bone disease or anaemia.

Infections with encapsulated germs should be managed proactively, and patients should be vaccinated against influenza, haemophilus influenza and pneumococcus. Intravenous bisphosphonates should be started or restarted at relapse, in combination with calcium and vitamin D supplementation. Local radiation therapy (20–40 Gy) may be required for local bone lesions in case of pain or imminent fracture. Anaemia should be treated with EPO (erythropoietin 40.000 UI per week, or darbepoetin 500 µg per three weeks) or transfusion [62]. Prevention of PN and thrombosis should follow the published guidelines [63].

Conclusions

Multiple myeloma can present a difficult diagnostic issue, as there are a wide variety of presenting symptoms. MM should be suspected in patients presenting signs of back pain combined with other systemic symptoms such as fatigue and weight loss, or back pain combined with abnormal blood tests. Confirmation of a MGUS and an increased (>10%) BM plasmacytosis are key determinants for the final diagnosis of MM. Despite significant advances in the management of MM, the disease remains incurable. Virtually all patients will develop relapsed disease, although strides in the field have provided opportunities for longer-term remissions.

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