ABSTRACT

Multiple myeloma (MM) is the second most common haematologic malignancy in the Western world, that typically starts as asymptomatic precursor conditions: monoclonal gammopathy of undetermined significance and smouldering MM where initiating genetic abnormalities, such as hyperdiploidy and translocations involving the immunoglobulin heavy chain, are already present. A small group of patients with asymptomatic precursor disease have high risk of progression, based on biomarkers of malignancy, and for these patients treatment may be considered. The introduction of immunomodulatory drugs, proteasome inhibitors and CD38-targeting antibodies have extended survival, but ultimately the majority of patients will die from their disease, and some from treatment-related complications. Disease progression and subsequent relapses are characterised by sub-clonal evolution, and increasingly resistant disease. MM patients present with hypercalcemia, renal failure, anaemia, and/or osteolytic bone lesions, and a detailed diagnostic work-up is needed to differentiate between symptomatic MM requiring therapy, and the precursor states. Risk stratification using both patient-specific (e.g. performance status) and disease-specific (e.g. presence of high-risk cytogenetic abnormalities) is important for prognosis and to define the best treatment strategy. Among current research strategies are the use of minimal residual disease (MRD) assays to guide therapy, refining immunotherapeutic approaches and intercepting disease early in smouldering myeloma.

INTRODUCTION

In multiple myeloma (MM), recent years have seen greater focus on understanding disease evolution from precursor conditions, increasing use of minimal residual disease for prognostication, and the continued fast-paced development of new therapies. Such therapies include both next generation agents of known classes of anti-myeloma drugs as well as agents with new mechanisms of action, most notable of all the new immunotherapies. Of key importance in MM management are supportive care measures that have to keep pace with the new treatments bringing unfamiliar toxicities, and survivorship challenges that come with extending survival without cure. In this seminar we provide a practical approach to understanding these latest developments, and their implications for how we manage this challenging malignancy in the real world.

BULLETED FAST FACTS

-Multiple myeloma (MM) is a plasma cell neoplasm that is the second most common hematologic malignancy in the Western world

-MM is virtually always preceded by an asymptomatic precursor condition: monoclonal gammopathy of undetermined significance (MGUS) and/or smouldering MM.

-MM is characterized by end-organ damage: hypercalcemia, renal insufficiency, anaemia, and bone destruction (CRAB criteria).

-Indications for treatment are based on presence of end-organ damage (CRAB criteria) or presence of at least one biomarker of malignancy (clonal BM plasma cells ≥60%, FLC ratio ≥100, or > 1 focal lesion on MRI).

-Risk stratification using both patient and disease features provides prognostic information and helps to define the best treatment strategy.

-Response to therapy is based on measurement of the M-protein in serum and urine, BM assessment of plasma cells and imaging of plasmacytomas or bone lesions.

-Achieving minimal residual disease (MRD)-negative status is associated with improved progression-free (PFS) and overall survival (OS)

-The introduction of novel agents such as immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and antibodies targeting CD38 has markedly improved survival however a small group of patients with ultra high risk disease continue to fare poorly.

- Newly diagnosed patients receive bortezomib or lenalidomide-based induction regimens, with the option of intravenous high-dose chemotherapy and autologous stem cell transplantation in fitter patients, while frailer, less fit, patient receive oral dose-adjusted protocols

- Relapse is usually detected as a rise in M-protein, and treatment is initiated for MM-related symptoms (CRAB features) or a rapidly rising M-protein

-Several regimens are available to treat relapse, selection is guided by patient features (age, frailty, organ function), disease characteristics (cytogenetics), patient preferences (oral or IV treatment), previous treatment (response, toxicity), and reimbursement/availability issues.

-Supportive care is important to prevent and manage side effects, so as to minimise delays or discontinuations, and to manage treatment and disease burden

CONTENTS

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1. EPIDEMIOLOGY, RISK FACTORS AND CLINICAL COURSE

Multiple myeloma (MM) is a blood cancer of monoclonal plasma cells that accumulate in the bone marrow(BM) and produce a monoclonal immunoglobulin(M-protein). MM is complicated by organ dysfunction: hypercalcemia, renal insufficiency, anaemia, and bone destruction(CRAB). MM accounts for 1% of neoplastic diseases, and is the second most common hematologic malignancy in the Western world, incidence 4.5-6/100,000/year and median age at presentation around 70 years. Incidence is higher in Western European, North American, and Australasian populations, and lower in Oceania, Asia, and sub-Saharan Africa, possibly due to variation in diagnosis[1]. From 1990 to 2016, there was a 126% increase in incidence of MM globally, due to population growth, an aging world population, and increased age-specific incidence rates[1]. Risk factors for development of MM include obesity, chronic inflammation, and exposure to pesticides, organic solvents, or radiation. Inherited genetic variants also contribute to the development of MM[2,3]. A recent report summarises both inherited and societal influences accounting for racial disparities in incidence and outcomes of MM and precursor conditions[4].

The use of novel agents such as proteasome inhibitors(PIs), immunomodulatory drugs(IMiDs), and antibodies targeting cell surface molecules, together with high-dose therapy and autologous stem cell transplantation(ASCT) in younger patients, has markedly improved outcome of MM patients[5]. Median overall survival in younger and fitter MM patients is currently estimated to be approximately 10 years, and in older non-transplant eligible patients, 4-5 years[6,7]. The majority of MM patients experience multiple relapses of their disease. Each subsequent remission is of increasingly shorter duration and ultimately patients will die from disease and/or treatment-related complications.

2. PATHOGENESIS, GENOMICS AND THE MARROW MICROENVIRONMENT

The initiating event driving malignant development is either the acquisition of hyperdiploidy or a translocation involving the immunoglobulin heavy chain gene locus[8]. These are clonal events found in almost all cells and present in the precursor conditions monoclonal gammopathy of undetermined significance (MGUS) and smouldering myeloma (SMM). Aetiologic translocations place oncogenes under the control of the strong immunoglobulin heavy chain(IgH) gene enhancer (t(4;14): *MMSET/FGFR3*; t(6;14): *CCND3*; t(11;14): *CCND1*; t(14;16): *MAF;* and t(14;20): *MAFB)*[9]. Additional genetic events are found in subclonal populations, with increased frequency as disease evolves from precursor conditions to MM. Acquired genetic events include copy number abnormalities, secondary translocations and somatic mutations, many of these converge to dysregulate the cell cycle **(Figure 1)**[10].

Copy number abnormalities result in chromosomal regions of loss or gain. Loss of tumour suppressor genes results from del(1p): *CDKN2C/FAF1/FAM46C*; del(11q): *BIRC2/BIRC3*; del(13q): *RB1/DIS3;* and del(17p): *TP53*. Gain(1q) is found in around 40% of patients, frequently in association with t(4;14). Common secondary translocations involve MYC either via t(8;14) or not involving the IgH gene. Somatic mutations are highly variable between patients[13], and occur most frequently in genes of the RAS/MAPK pathway, around 50% of patients have a mutation (KRAS 22%, NRAS 17%, BRAF 8%). Other commonly mutated genes include FAM46C and DIS3 in around 10% of cases each[14].

Other signaling pathways affected include the NFkB pathway, affected by copy number loss, mutation and translocations and the PI3K pathway, that is dysregulated in the absence of genetic change[15]. Apoptotic pathway dysregulation occurs, with Bcl-2 dependency in patients with t(11;14) and Mcl-1 dependency in others[16]. Normal plasma cell differentiation signaling is altered with upregulation of IRF4 via a positive autoregulatory loop and loss of the negative feedback to MYC expression via PRDM1[17]. Epigenetic dysregulation plays a key role in myeloma. MMSET, upregulated by t(4;14) and present in up to 15% of patients, is a histone 3 lysine 36 methyltransferase and is associated with a distinct DNA methylation pattern[18].

Acquired events collaborate with the background driver, with differing frequencies in each aetiologic subgroup[12,20]. Both initiating and acquired genetic events have important prognostic and therapeutic implications with adverse outcome particularly associated with t(4;14), t(14;16), t(14;20), gain(1q) and del(17p)[21,22]. The loss of TP53 from both alleles, eg. presence of del(17p) and mutation of the second allele, associates with dismal outcomes[11]. Major genetic change occurs early in disease evolution with fewer changes identified between SMM and MM than between MGUS and SMM[23]. Thus, the transition to disease requiring therapy may be partly driven by changes in the BM microenvironment. In this context the BM is the Darwinian selective pressure exerting influence over the clonal population.

Ultimately there is co-evolution of the MM clone and the BM microenvironment with an increase in tumour promoting immune cells and loss of anti-tumour immunity as disease evolves. The influence of the microenvironment is exemplified by studies demonstrating spatial clonal differences in samples taken simultaneously from different BM sites in a patient[24]. An association is also seen between immunoparesis and disease progression from SMM to MM, suggesting loss of immune function and microenvironmental control of clonal expansion[25]. Multiple components of the BM microenvironment may be involved, eg. mesenchymal stromal cells, B-cells, T-cells, osteoclasts and adipocytes[26,27].

Damage to the structure of bone itself is a major cause of morbidity in MM, driven by disruption of the balance between bone-resorbing osteoclasts and bone-repairing osteoblasts that constitute physiological bone-remodeling processes[28]. Tumour cells secrete osteoclast-activating factors including RANK ligand and IL-6 and osteoblast inhibitory factors eg. DKK1 and sclerostin. This leads to bone loss and a feedback loop driving further MM cell proliferation and immune suppression resulting from the release of IGF-1 and TGF-beta during bone resorption[29].

3. PRESENTING SYMPTOMS, DIAGNOSTIC WORK-UP AND PROGNOSTIC MODELS

Patients are sometimes identified on the basis of a M-protein(paraprotein) on routine blood testing, although most patients present with signs and symptoms of organ damage (bone pain and fractures, infections, anaemia, renal failure and hyperviscosity). A detailed diagnostic work-up of patients with MGUS/SMM is needed to differentiate between MM and asymptomatic precursor conditions, based on clinical, biochemical, and radiological criteria **(Table 1)**[30,31]. Indications for treatment are based on presence of end-organ damage or at least one biomarker of malignancy**.**

At the time of MM diagnosis, a detailed medical history, physical examination, and laboratory studies should be performed **(Supplementary Table 1)**. Evaluation of MM bone disease requires cross

sectional imaging. Low-dose whole-body computed tomography is recommended, as it is fast and more sensitive than plain radiography[32]. Recent imaging guidelines recommend functional imaging techniques such as ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), or diffusion weighted magnetic resonance imaging (MRI) for response assessment. Dedicated whole spine MRI may be required for evaluation of spinal cord compression[32]. BM sampling is required to assess level of infiltration, either by histopathology on the biopsy, or morphology/flow cytometry on the BM aspirate. Cytogenetic analysis by fluorescence in situ hybridization(FISH) on purified MM cells, should include at least tests for the high risk lesions t(4;14), t(14;16), and del(17p)[33]. Gene expression and mutation panels can provide further prognostication, but these are not available routinely in most centres.

Clinical outcome of patients with MM depends on several factors **(Supplementary Table 2)**, including intrinsic tumor cell characteristics (cytogenetic abnormalities, gene expression profile, extramedullary growth, LDH)[33,34], tumor burden (beta2-microglobulin, low platelet count), and patient features (age, comorbidities, frailty)[35]. Outcome is also dependent on depth of response to therapy. Models that combine patient and disease characteristics have been constructed, because individual prognostic factors do not capture the full heterogeneity in outcome. The original ISS staging system, based on serum albumin and beta2-microglobulin levels, reflects tumor burden and patient condition[36]. This has been updated into the revised ISS staging system that includes information on the presence of high-risk genetic lesions (t(4;14), t(14;16), and/or del(17p)), LDH **(Supplementary Table 3)**[37]. Inclusion of more detailed genetic/molecular information may provide further prognostic information, such as co-occurrence of multiple adverse cytogenetic lesions, eg biallelic disruption of *TP53* that is associated with particularly poor outcomes[12].

4. DISEASE MONITORING INCLUDING ASSESMENT OF MRD

Response to therapy is based on measurement of the M-protein in serum and urine combined with BM assessment of plasma cells **(Supplementary Table 4)**. Minimal residual disease (MRD) assessment of BM is generally only performed in the context of clinical trials, but evidence from current trials may support its use to direct treatment in the near future. Cross-sectional imaging is repeated during follow-up when clinically indicated, e.g. as part of response assessment in extra-osseus tumours, or in patients with soft tissue plasmacytomas, or in case of signs of progression (e.g., pain or increase in serological parameters).

Response to therapy is an important prognostic factor, with complete response (CR) or stringent complete response (sCR) translating into improved long-term survival[38,39]. However, select patient subgroups, including those with MGUS-like profiles, may experience long-term survival without achieving CR[39,40]. As a refinement of CR, sensitive methods for detecting MRD in the BM, such as multiparameter flow cytometry(MFC) or next generation sequencing(NGS), are increasingly employed. Achieving MRD-negative status is consistently associated with improved PFS and OS in NDMM patients, regardless of transplant or genetic risk[39,41-43]. While maintenance/continuous therapy can maintain MRD-negativity[41,44], the impact of MRD status will differ depending on whether patients remain on treatment. Although there is no consensus on optimal timepoints or frequency of MRD assessment, sustained MRD-negativity(≥12 months)[45], is probably the best surrogate for prolonged survival[45,46]. MRD is now incorporated in the updated International Myeloma Working Group (IMWG)

response criteria **(Supplementary Table 4)**[45]. In the future, it is likely that regulatory authorities will consider MRD status as a surrogate for estimating survival, accelerating approval of new drugs[47]. Several trials are ongoing to define the potential role for MRD to inform treatment decisions, e.g. the need for consolidation, or to guide type and duration of maintenance treatment.

MRD monitoring of BM, however, fails to detect extramedullary disease and can be falsely negative due to patchy involvement of BM[47]. Thus, functional imaging techniques such as FDG-PET/CT are required to assess residual disease outside the BM, and complement BM-based MRD assessment after therapy[48]. PET/CT scans may, however produce false positive (e.g., infection, inflammation) or false negative results (hyperglycemia or low expression of hexokinase-2[49]).

5. MGUS AND SMM: MANAGEMENT AND RISK MODELS

There is good evidence that MM is always preceded by the precursor conditions MGUS and SMM[50]; these are characterized by the absence of signs or symptoms related to MM or other lymphoproliferative diseases; only 5-7% of MGUS patients, and around 50% of SMM will develop MM over the first 5 years from diagnosis[51,52]. Careful assessment of disease bulk and organ function using the same diagnostic work up as for MM is recommended, and cross-sectional imaging with whole body CT or MRI is advised for high risk MGUS and all SMM patients[32]. In order to mitigate the risk of progression and enable early diagnosis, long-term follow up is advised, adjusted according to risk (see below) and life expectancy[53] **(Figure 2)**. Rarely, the MGUS or SMM clone itself is clinically relevant, e.g. due to cytokine secretion(POEMS syndrome) or the physico-chemical properties of the M-protein (light-chain amyloidosis, monoclonal gammopathy of renal significance, MGRS) or auto-antibody activity (e.g. IgM neuropathy)[54]. Clone-directed therapy with anti-MM agents may be indicated in cases of aggressive and disabling disease[55].

In 2014, a small subset of ultra-high-risk SMM patients was reclassified by the IMWG as MM, and recommended to start therapy, without waiting for organ damage to occur. These patients have high risk of progression in 2 years (>70%) and are identified by ≥60% BM plasmacytosis, presence of >1 focal lesion on MRI, or FLC ratio≥100 (biomarkers of malignancy; **Table 1**)[31]. Excluding ultra-high risk patients, models to aid prediction of the risk of progression in MGUS[56] and SMM[57] patients are required **(Figure 2).** The 20-20-20 risk model for SMM is based on cut off values for serum M-protein(20 g/L), involved to uninvolved serum free light chain ratio(20) and bone marrow plasma cell infiltration(20%), as independent risk factors. In this model, patients with ≥2 risk factors had a 2-year progression rate of 46%, and may be candidates for clinical trials. Two studies reported that early intervention with lenalidomide with or without dexamethasone in intermediate or high-risk SMM delayed progression to symptomatic disease and resulted in longer OS, compared to observation only[58,59]. An alternative strategy of intensive combination therapy followed by high-dose melphalan and autologous stem cell transplantation(ASCT), resulted in a high rate of CR and MRD-negativity, but actual cure remains uncertain[60]. As yet, no treatment is approved for SMM.

6. TREATMENT OF MYELOMA

Proteasome inhibitors(PIs) and immunomodulatory drugs(IMiDs) are the current mainstay of therapy and usually comprise the 'backbone' to which newer agents are added in clinical trials. Steroids, in the form of dexamethasone or prednisolone are invariably included. The fourth class of agent that is fast

becoming a key component of relapse and frontline therapies is CD38-targeting antibodies (**Supplementary Tables 5-6**). The main agents used, together with their licensed indications and main toxicities are detailed in **Table 2**.

Frontline therapy: Use of autologous stem cell transplantation in younger fitter patients.

Although no treatment is truly curative, the aim of first-line therapy is to induce a deep response, because depth of response correlates with longer time to relapse, and overall survival[39]. The largest body of evidence for any single strategy to achieve this is in the use of induction therapy followed by ASCT, hence is standard of care in most countries in patients who are fit[61,62]. Evidence is accruing, however, to support the alternate strategy of deferring ASCT until relapse, especially in patients achieving deep responses[63]. In a recent RCT to evaluate the benefit of ASCT vs. chemotherapy, patients allocated to the ASCT arm enjoyed longer PFS, but survival outcomes are similar[61]. Nevertheless, ASCT remains standard of care in many parts of the world. Selection of patients for ASCT is based on organ function, age, performance status, and response to induction therapy, as those with refractory or progressive disease do not benefit from ASCT[64]. Prior to ASCT, patients receive several cycles(3-6) of induction with a multi-drug regimen, after which hematopoietic stem cells are mobilized into the peripheral blood, harvested and frozen down. These stem cells are then re-infused 1-2 days after high-dose chemotherapy (usually melphalan), hence autologous stem cell transplantation(ASCT). Many centres aim to harvest sufficient stem cells to support a second ASCT, either as a tandem procedure or at relapse (see below).

Induction regimens

Current standard of care is a bortezomib regimen, combined with dexamethasone, and an IMiD (thalidomide or lenalidomide, VTd or VRd) or cyclophosphamide (VCd). Overall responses (defined as at least PR, **Supplementary Table 4**) to such regimens are generally >80% and around 40-50% of patients also achieve at least a VGPR. Following ASCT, responses increase by around 10-20%[61].

Recent studies report high response rates to the second generation PI, carfilzomib, in combination with lenalidomide and dexamethasone as induction prior to ASCT[65], but this remains unlicensed. The benefit of adding the CD38 antibody, daratumumab, to VTd, has recently been reported, with higher CR rates of 39% versus 26% and an improvement in progression-free survival (PFS)[66]. The 4-drug regimen, daratumumab-VTd was recently licensed by the FDA (Sept 2019) and by EMA (Jan 2020) for treating transplant eligible NDMM. Addition of daratumumab to VRd in the phase II GRIFFIN trial produced deeper disease responses (measured as stringent CR, sCR) compared to VRd[67].

The benefit of ASCT delivered as part of a first-line regimen has recently been re-visited in the light of high rate of, and deep responses to, newer induction regimens. The most recently reported are the IFM2009/DFCI Phase 3 trial, and the EMN02 trial[61,62]. Both trials used bortezomib-based induction followed by randomisation to ASCT or chemotherapy as consolidation and both studies employed lenalidomide maintenance. Both response depth and PFS was superior in the ASCT arm, however OS remains comparable, at the current follow up.

Consolidation and maintenance following ASCT

Today, the deepest measure of response, MRD-negativity, is considered to be the goal of treatment, especially in the context of younger fitter patients undergoing ASCT[39,41,42]. Thus, several approaches to deepen and maintain disease response after ASCT have been studied.

Consolidation consists of limited duration treatment, usually with same induction regimen to deepen response, and hence improve PFS and OS. The benefits of consolidation remain contentious, with divergent evidence from recent randomised trials[62,68], and likely depend on the induction regimen and the depth of response achieved. An alternate strategy is to proceed to a second transplant around 3 months after the first (tandem ASCT), an approach that may benefit patients with genetic high risk, as these patients respond well initially, but relapse early with resistant disease. The benefit of tandem ASCT in high risk disease is not, however, supported by all published studies[62,68].

Maintenance therapy, in the form of continuous treatment usually with a single agent, is administered in order to improve response, delay disease progression and extend survival. Lenalidomide is licensed for maintenance following ASCT, based on the results of several phase 3 studies which demonstrated a prolonged PFS and OS with lenalidomide compared to observation/placebo. There is some evidence for efficacy even in genetically high-risk disease that was not seen in the earliest studies but became apparent in the Myeloma XI study which included a larger number of genetically characterised patients [69,70]. A meta-analysis of bortezomib as maintenance therapy revealed a benefit for both PFS and OS[71], while ixazomib has shown efficacy as single agent maintenance therapy[72] and combinations approaches are under investigation. Outside clinical trials, the practice is emerging of adding bortezomib to lenalidomide maintenance therapy for high risk patients[63].

Frontline treatment approaches without ASCT

ASCT-sparing protocols have hitherto generally been tailored to older patients not deemed fit for high dose chemotherapy however, recent use of highly effective frontline regimens have led to an increasing trend to delay ASCT until relapse, especially in patients achieving a deep response to initial therapy. In a series of 1000 patients receiving VRd induction, 18% were allocated to deferred ASCT, on the basis of achieving deep responses (≥VGPR), and enjoyed a PFS of 74.3 months, compared to 63 months in the ASCT group, albeit with the majority receiving maintenance with lenalidomide (bortezomib added for high-risk)[63].

For older patients who are not deemed transplant-eligible, outcomes have not seen the same improvements as for younger patients over the last 10-15 years, largely due to poorer tolerability of multi-drug regimens[73]. This is beginning to change, due to better supportive care, greater use of frailty-adjusted treatment and development of more effective and tolerable regimens, e.g. modification of bortezomib scheduling and the use of the VRd-lite regimen[74]. The use of ASCT in the older fitter patient (aged 65-75) continues to be explored, and good results are seen with careful patient selection[75]. Current non-ASCT regimens used in fitter older patients are generally triplet regimens, e.g. VRd, VCP, VMP (**Table 2**). The additional benefit of adding a CD38 antibody has led to the recent licensing of the quadruplet, daratumumab, bortezomib, melphalan and prednisolone (Dara-VMP)[76], as well as the triplet, daratumumab plus lenalidomide-dexamethasone (Dara-Rd)[77]. Substituting the second generation PI, carfilzomib (K) for bortezomib in VRd did not improve outcomes in standard-risk patients in one study to date, hence VRd remains the PI+IMiD triplet of choice in fit standard-risk patients[78]. Maintenance approaches have also been studied in the non-ASCT setting, with some evidence to support lenalidomide, as well as the CD38 antibody daratumumab and the oral proteasome inhibitor, ixazomib[63,76,79].

Treatment of the frail elderly patient

Performance status outweighs genetic risk in relative contribution to overall survival for patients over the age of 70[73]. Recently, attention has turned to the older frail patient, and the use of frailty tools and

geriatric assessments in this vulnerable patient group has provided data in support of dose and schedule-adjusted regimens, improving tolerability, treatment delivery and clinical outcomes[35]. Clinical trials stratifying treatment intensity according to fitness and the remarkable good tolerability of newer treatments such as the CD38 antibodies signal a step change in the prospects for these patients.

Treatment of relapse

For many patients, relapse is inevitable, and not all patients remain candidates for further treatment[80]. Disease relapse is often heralded by a rise in the M-protein or light-chain, called a biochemical relapse if there are no clinical symptoms. Treatment should be started in case of MM-related symptoms (CRAB features) or a rapid M-protein increase (doubling in two months). With the growing number of therapeutic options, treatment selection and sequencing is challenging. The optimal sequence and choice of agents is not established, and choice of therapy depends on several factors, including patient features (age, frailty, BM reserve, comorbidities, performance status), disease characteristics (cytogenetic risk, rapid increase in M-protein), patient preferences (oral or IV), previous treatment factors (response, toxicity), and reimbursement/availability issues[81].

First relapse

Lenalidomide-dexamethasone (Rd)[82,83], bortezomib-dexamethasone (Vd)[84], and carfilzomib-dexamethasone (Kd)[85,86] are established doublet regimens for the treatment of RRMM. The ENDEAVOR study, a head-to-head comparison of Vd with Kd in patients at first to third relapse, showed a higher response rate, and longer PFS and OS, in patients treated with Kd[85,86].

Randomized trials have shown that adding a third drug, with a different mechanism of action, to these doublet regimens improves depth of response and PFS, and in some studies with more mature follow-up also OS. There are currently four approved lenalidomide-based triplet regimens, including 2 with a proteasome inhibitor (carfilzomib, KRd[87], and oral ixazomib, IRd[88]). Monoclonal antibodies can also be effectively combined with Rd. Elotuzumab, an antibody directed against SLAMF7, has no single-agent activity[89], but improves PFS in combination with Rd, compared to Rd alone[90,91]. Daratumumab, a first-in-class anti-CD38 antibody has single-agent activity[92], and improves PFS and response rates when combined with Rd[93].

Many patients experience first relapse having received, or while still receiving lenalidomide therapy, hence lenalidomide based (Rd) salvage may not be appropriate. Three bortezomib-based triplets are approved for the treatment of relapsed/refractory MM based on adding daratumumab[94], panobinostat[95] (a pan-deacetylase inhibitor), or pomalidomide[96] to the Vd backbone. The Kd combination also provides a backbone for the incorporation of additional agents, such as daratumumab or isatuximab[97,98]. Details on these triplet regimens are in **Supplementary Tables 7-8**.

Cyclophosphamide-based triplets are not approved, but relatively affordable and widely used, eg. the fully oral triplet pomalidomide-cyclophosphamide-dexamethasone (PCd) was effective and safe as second-line treatment in RVD-treated patients[99]. In addition, it was recently shown that the triplet carfilzomib-cyclophosphamide-dexamethasone (KCd) induces higher responses compared to VCd in patients with first relapse[100].

Patients who received frontline bortezomib-based therapy, are typically treated at the time of relapse with a lenalidomide-containing regimen, while patients who develop progression during lenalidomide treatment are switched to a proteasome inhibitor-based treatment **(Figure 3)**[81]. There is also increasing evidence that pomalidomide-based triplets, such as pomalidomide combined with bortezomib-dexamethasone, are effective in patients with lenalidomide-refractory disease **(Figure 3)**[96]. After reinduction therapy, consolidation with high-dose therapy plus ASCT should be considered at the time of first relapse in patients who did not receive upfront ASCT, or after a previous ASCT if initial response duration was at least 24 months[101]. Allogeneic stem cell transplantation may be considered in high-risk patients with early relapse after ASCT, ideally in context of a clinical trial. Patients relapsing early (≤12 months) after first-line therapy tend to have resistant disease and a short overall survival of around 24 months[102,103]. Many but not all can be identified by the presence of high-risk genetic lesions (especially >1).

Second relapse and beyond

Many patients suffer repeated relapses, responding to re-treatment, often with change in drug class[80]. Patients with lenalidomide and bortezomib(double)-refractory disease have a poor prognosis, and may benefit from regimens containing pomalidomide, daratumumab, or carfilzomib. Selection of drugs is largely driven by type of prior therapy and duration of response. Pomalidomide-dexamethasone (Pd) is effective in about 30% of double-refractory patients[104], and responses are generally improved when combined with a third anti-MM drug (**Supplementary Table 9**)[105-109]. Combinations of Pd with daratumumab or elotuzumab are approved in this setting[106,108]. Furthermore, the FDA and EMA recently approved isatuximab combined with Pd[109]. Where antibodies are not available, cyclophosphamide can be effectively combined with Pd[105]. Although daratumumab is increasingly combined with other agents, it is also approved as monotherapy in patients with advanced MM, and may benefit some patients with multiply relapsed disease[92,110]. Carfilzomib-dexamethasone can also be effective in double-refractory patients[111].

Triple-class refractory MM

Patients who develop disease refractory to IMiDs, PIs, and CD38-targeting antibodies (triple-class refractory) have an OS of only a few months[112]. Selinexor (oral selective Exportin 1 inhibitor) plus dexamethasone is effective in about a quarter of triple-class refractory patients, and has recently been approved by the FDA[113]. These patients may also benefit from belantamab mafodotin, an FDA/EMA-approved BCMA-targeting antibody-drug conjugate, which induces an overall response of 30% with keratopathy and thrombocytopenia as most common adverse events[114]. Heavily pretreated patients may also benefit from retreatment, which can be considered after long-lasting remission, as previously used agents can be given in different combinations. Novel agents can also be combined with traditional cytotoxic agents such as cyclophosphamide, anthracyclines or bendamustine[115]. Alternatively, patients with advanced disease can be enrolled in clinical studies evaluating new agents with novel mechanisms of action.

7. SOLITARY PLASMACYTOMA AND PLASMA CELL LEUKEMIA

Solitary plasmacytoma

Solitary plasmacytomas usually arise in marrow bearing bone (ribs, vertebrae, pelvis, femurs) with or without extra-osseus extension. [116]. Extramedullary plasmacytomas (EMP) have no bone involvement, and occur most commonly in the head and neck, GI tract and lungs. Diagnosis is based on tissue evidence of monoclonal plasma cell infiltrate; it is important to exclude the presence of occult MM hence investigations should include BM examination, and cross-sectional imaging (PET-CT or WB-MRI). Around 50% of SBP but only 30% of EMP will progress to MM within 10 years, such estimates may change as techniques for detecting occult disease improve. Flow-cytometric detection of low levels of plasma cells with aberrant phenotype in the BM, for example, correlates with increased risk of developing symptomatic MM[117,118]. Current standard of care remains local radical radiotherapy, followed by watchful waiting.

Extramedullary disease and plasma cell leukemia

Extramedullary involvement is rare in NDMM, but more common in multiply relapsed patients, and carries a poor prognosis. Extramedullary disease results from hematogenous spread of MM cells, and is characterized by presence of soft tissue masses in extraosseous locations (e.g. in skin, lymph nodes, or brain), pleural effusions, or leptomeningeal disease[119]. Plasma cell leukemia (PCL) can be considered the most extreme variant of extramedullary MM, and is characterized by the presence of $>2x10^9$/L peripheral blood MM cells or plasmacytosis accounting for >20% of the white cell count. Primary PCL arises *de novo* without evidence of preexisting MM, while secondary PCL is a leukemic transformation of end-stage MM. Primary PCL has an aggressive clinical presentation and poor prognosis with high early mortality due to disease-related complications[120]. Although outcome of primary PCL has improved due to introduction of ASCT and combination therapy with novel agents, survival is still inferior to that observed in newly diagnosed MM[120].

8. SUPPORTIVE CARE

Myeloma patients suffer much disease and treatment burden, causing morbidity and mortality. Disease complications, such as infections, bone disease and gastrointestinal upset, lead to treatment delays or discontinuation, reducing disease free survival[121-124]. Infections, cardiovascular disease, and renal failure are major causes of early death in MM[125,126]. Before the introduction of novel agents, around 10% of patients died within 60 days of diagnosis due to disease or therapy-related complications[125]. Therapy with novel agents is associated with substantially lower early mortality, probably as a result of lower toxicity and greater efficacy[124]. Careful monitoring, as well as dose adjustments in frail patients[35], to prevent the development of unacceptable toxicity, is of critical importance to reduce early mortality and improve survival. Organs affected are shown and discussed in **Figure 4,** and interventions to manage end organ damage and drug toxicity are discussed below.

Bone disease

Bisphosphonates or denosumab are initiated in MM patients with active myeloma requiring therapy. Intravenous(IV) pamidronate or IV zoledronic acid have comparable efficacy in reducing skeletal

related events (SRE)[127], while oral clodronate is less effective[128]. Osteonecrosis of the jaw (ONJ) is a recognised toxicity associated with bisphosphonate use, and they should be avoided in renal impairment (CrCl <30 ml/min)[129]. Denosumab, a RANKL neutralizing antibody, can be administered to patients with renal failure[130]. Local radiation therapy can be helpful for painful bone lesions, while surgery may be required for fixation of fractures, or pre-emptively to prevent fractures in long bones with large lytic lesions[129]. Vertebral augmentation (balloon kyphoplasty, vertebroplasty) may provide pain relief in patients with symptomatic vertebral fractures[129].

Infections

Bacterial infections occur most frequently in patients with active MM who are starting therapy[123,131] and antibacterial prophylaxis should be considered, especially during the first 3 months of treatment initiation. A recent trial in NDMM showed that 12-weeks treatment with levofloxacin reduced febrile episodes and death, without development of antibiotic resistance, when compared to placebo[132]. Sulfamethoxazole-trimethoprim prophylaxis is also commonly used and may also reduce febrile episodes and deaths[132]. Although, neutropenia is relatively rare at diagnosis[133], treatment may induce significant neutropenia, and cytopenias may develop in heavily pre-treated patients requiring schedule adjustment, and/or use of growth factors. Immunoglobulin supplementation may be useful in patients with recurrent bacterial infections and co-existing hypogammaglobulinemia[134]. Guidelines also recommend routine vaccination against influenza, *Streptococcus pneumoniae,* and *Haemophilus influenzae* type B[135], ideally during periods of optimal disease control[135]. Live vaccines are generally contraindicated. Proteasome inhibitors impair antigen-specific T-cell functions and are associated with varicella zoster virus (VZV) reactivation. VZV prophylaxis is mandatory during treatment with PIs[135], and should also be considered with monoclonal antibody-based therapy and following ASCT. Hepatitis B reactivation is also recognised following PI, IMiD and daratumumab therapy and all MM patients should undergo serology tests prior treatment initiation. Those with active hepatitis should be managed in conjunction with a hepatologist and those with evidence of past infection (e.g. Hepatitis B core antibody positive) require prophylaxis to prevent reactivation. Novel diseases, such as the coronavirus disease 2019 (COVID19) pandemic caused by the SARS-COV-2 virus, pose a particular threat to immunosuppressed MM patients until vaccines become available. Steps to avoid exposure to infection are critical and may require alterations to anti-MM therapy and prophylaxis[136].

Thromboembolic and cardiovascular disease

Thromboprophylaxis is recommended for patients on IMiD treatment: aspirin in low-risk patients and, in patients with >1 risk factor, low-molecular weight heparin (LMWH) or direct oral anticoagulants; after 4 months, a switch to aspirin can be considered[137-139]. If a patient experiences a thromboembolic event, anticoagulation therapy should be started with therapeutic dose LMWH. Direct oral anticoagulants are reported to be non-inferior to LMWH with respect to the composite outcome of recurrent VTE or major bleeding in cancer patients[140].

Cardiovascular disease may be related to the underlying plasma cell disorder (AL amyloidosis, anemia, and renal dysfunction) or to therapy. Cardiotoxicity is more frequently observed in elderly patients and those with pre-existing cardiovascular disorders[137]. Anthracyclines can reduce cardiac contractility and IMiDs may induce arrhythmias. Carfilzomib therapy is associated with a risk of hypertension,

pulmonary hypertension, and cardiac failure[85,141], and these patients should be monitored for hypertension and fluid overload[137].

Peripheral neuropathy

Treatment related peripheral neuropathy usually presents with symptoms of tingling, pain, or numbness in hands and feet. Prompt identificiation and cessation or modulation of treatment can prevent permanent damage. First in class immunomodulatory agents and proteasome inhibitors (thalidomide and bortezomib) are often implicated, and can cause both sensorimotor and autonomic neuropathy. [142]. A change of clinical practice from intravenous to subcutaneous bortezomib administration, and from bi-weekly to once-weekly schedule, has resulted in a lower rate of neuropathy[143,144], while partnered dexamethasone dosing may also help[145]. Fortunately, neuropathy is not a class effect of either immunomodulatory drugs or proteasome inhibitors, since lenalidomide, pomalidomide, carfilzomib and ixazomib are associated with a low rate of neurotoxicity[85]. Pharmacological interventions for neuropathy include neuroleptic agents, anti-depressants, anti-epileptic medications, or topical pain medication.

Renal impairment

The presence of renal failure at diagnosis is associated with shorter survival[121,125], probably due to an association with more advanced disease, lower recommended starting doses of anti-MM agents, and higher toxicity leading to dose reductions and/or drug discontinuations[146]. Reversal of renal impairment is associated with improved prognosis. Anti-MM therapy should be initiated without delay in patients presenting with acute renal impairment to rapidly reduce light chain load on the kidney. Bortezomib pharmacokinetics are unaffected in renal failure, and bortezomib-based therapy improves survival and renal function in MM patients presenting with renal failure, including those requiring dialysis[121,146,147]. Other anti-MM agents can also be effective in renal failure, but dose reduction is required for several **(Table 2)**. The evidence base for plasma exchange or the use of mechanical filters to rapidly reduce free light chain levels remains unclear[148-150].

9. NEW AGENTS AND FUTURE THERAPIES

New therapies with novel mechanisms of action are still needed for patients with disease refractory to all available approved agents, and for patients presenting with high-risk disease. Improved understanding of molecular abnormalities underlying disease initiation and progression and of tumor cell interactions with the protective microenvironment, enabled the development of new agents, including biomarker-based, personalized, therapeutic interventions for the treatment of specific molecular subtypes. The combination of these novel drugs with either conventional or other new drugs with complementary modes of action will be crucial to prevent outgrowth of resistant clones.

New anti-MM treatment approaches that show particular promise include several innovative immunotherapies, such as chimeric antigen receptor (CAR) T-cells, antibody-drug conjugates, and bispecific antibodies, some of which have demonstrated notable activity as single agents **(Supplementary Table 10)**. Many of these new agents target B-cell maturation antigen (BCMA), a

member of the TNF receptor superfamily that is highly and specifically expressed on plasma cells, including MM cells[151].

10. MANAGING MYELOMA IN THE REAL WORLD

Recent rapid pharmacological and technological developments have resulted in marked improvement in patient survival but, with increasing treatment costs, and, on a global level, there are marked differences in availability and reimbursement of the newer drugs due to economic constraints. [1]. Clinical trial data advance clinical practice and product licensing but need to be supplemented with real world evidence to provide more clarity about benefit, toxicity and tolerability, treatment duration, and longer term effects[152,153]. We also need real world information about patient groups not traditionally eligible for clinical trials (non-secretory disease, organ impairment, frailty, other malignancy). Better use of resources will come from using knowledge of disease biology, and MRD technology, to inform duration and intensity of treatment. Use of biomarkers, e.g. levels of anti-apoptotic proteins, to identify patients for selected treatments (e.g. Bcl-2 antagonists) will help reduce toxicities and healthcare costs by tailoring treatment to selected patient subgroups. Finally, increasing numbers of MM survivors warrant research into strategies to deal with cumulative disease and treatment burden, and aid return to good psychosocial and economic functioning. Initiatives such as new models of care and exercise programs require collaborative multi-disciplinary work to maximise long term outcomes[154].

Search strategy and selection criteria

We searched PubMed and the websites of major conferences (the American Society of Hematology, American Society of Clinical Oncology, and the European Haematology Association) for papers and abstracts published in English, that reported preclinical or clinical studies in multiple myeloma or related plasma cell disorders. We used the search terms “myeloma”, “multiple myeloma”, “MGUS”, “monoclonal gammopathy of undetermined significance”, “smoldering multiple myeloma”, and “primary plasma cell leukemia”, without restrictions on the date of publication. Literature was updated in July 2020, during the revision process for this Seminar. The final references list was generated on the basis of relevance and impact to the broad scope of this Seminar.

Conflicts of interest

KY: Research support from Janssen Pharmaceuticals, AMGEN, Sanofi Genzyme Oncology, Takeda Oncology; consultancy, honoraria, travel support from Takeda Oncology, Janssen Pharmaceuticals, Sanofi Genzyme Oncology, Roche Pharmaceuticals, consultancy from Autolus.

CP: Amgen – consultancy, honoraria, travel support; Takeda Oncology – consultancy, travel support; Janssen – honoraria, travel support; Celgene Corporation – consultancy, honoraria, travel support.

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Tables

Table 1. Diagnostic criteria for MGUS, SMM and MM[31]

Characteristic	MGUS	SMM	MM
M-protein and clonal BM plasma cells	M-protein <30 g/l, and urinary M-protein <500 mg/24 h, and clonal BM plasma cells <10%	M-protein ≥30 g/l, urinary M-protein ≥500 mg/24 h and/or clonal BM plasma cells ≥10 to <60%	Clonal BM plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
Myeloma-defining events: Biomarker of malignancy* or end-organ damage**‡	no	no	yes

*Biomarker of malignancy: clonal BM plasma cells ≥60%, FLC ratio ≥100, or > 1 focal lesion on MRI (each lesion must be 5 mm or more in size)

**End-organ damage that can be attributed to the underlying plasma cell disorder includes:

-Hypercalcemia [serum calcium >0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)]

-Renal insufficiency [creatinine clearance <40 ml/min or serum creatinine >177 µmol/L (>2 mg/dL)]

-Anemia [hemoglobin value of >20 g/L (>1.25 mM) below the lower limit of normal, or a hemoglobin value <100 g/L (<6.2 mM)]

-Lytic bone lesions (one or more osteolytic lesions on skeletal radiography, CT, or PET-CT (≥5 mm in size)). If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

‡Patients may present with renal failure that is not related to the plasma cell disorder, but the result of other underlying conditions that are prevalent in elderly patients such as diabetes and hypertension. Similarly, primary hyperparathyroidism should be considered in case of hypercalcemia; nutritional deficiencies for anemia; and metastatic carcinoma for lytic bone lesions.

Abbreviations: BM, bone marrow; FLC ratio, involved:uninvolved serum free light chain ratio; CT, computed tomography; PET-CT, positron emission tomography-computed tomography.

Table 2. Classes of drugs licensed for use in the treatment of multiple myeloma

Agent and mode of action	Route of administration	Licensed indications	Common regimens	Common side effects / caution
Alkylating agents				
Melphalan Induces DNA cross-linking and DNA double-strand breaks	Oral or IV	Treatment of myeloma, oral or IV	Melphalan (oral), prednisolone +/- thalidomide or bortezomib (MPT, MPV) High-dose melphalan (200 mg/m^2 IV) as conditioning for stem cell transplantation (SCT), lower doses for less fit patients and also as part of conditioning in reduced intensity allogeneic SCT	-Bone marrow suppression -Infections -Mucositis with high-dose melphalan -Increased risk of second primary malignancy -Dose reduction in renal impairment
Cyclophosphamide Formation of DNA crosslinks leading to apoptosis; at low (metronomic) doses also immune stimulatory activity and antiangiogenic effects	Oral or IV	First-line and relapse treatment and for peripheral blood stem cell mobilisation	Combination therapy with dexamethasone and IMiDs, eg CTD, CRD, and with PI's eg VCD, VCP and KCD	-Bone marrow suppression -Infections -Hemorrhagic cystits -Adequate fluid intake -Mesna in case of high-dose cyclophosphamide (e.g., 2 g/m^2) -Dose modifications for neutropenia and thrombocytopenia
Steroids				
Dexamethasone Agonist of the glucocorticoid receptor	Oral or IV	First-line and relapse therapy	Used in combination with almost all anti-myeloma regimens, often as pulsed (daily for 4 days) or weekly dosing In acute spinal cord compression, may be used as single agent	-Infections -Hyperglycemia -Insomnia, psychiatric side effects -Dyspepsia, gastritis, gastric or duodenal ulcer

Prednisolone	Oral	First-line and relapse therapy	In place of dexamethasone in older patients, e.g. MPT or MPV	With prolonged use: suppression of the hypothalamic-pituitary axis, AVN, myopathy
Anthracyclines				
Doxorubicin Topoisomerase II inhibitor	IV	First-line and relapse therapy	PAD DT-PACE	-Heart failure -Increased risk of second primary malignancy -Myelosuppression and infections -Total cumulative dose should not exceed 550 mg/m^2 -Discontinue doxorubicin in patients who develop cardiomyopathy
Proteasome inhibitors (PI)				
Bortezomib 1st generation reversible boronic acid proteasome inhibitor	IV, SC	First-line therapy Relapsed disease	MPV, VCD, VTD, VRD, Vd dara-VMP Vd, VCD, VTD, Pano-Vd, dara-Vd, PVd	-Peripheral neuropathy -Thrombocytopenia -Diarrhea/constipation -Herpes zoster
Carfilzomib 2nd generation epoxyketone PI that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome	IV infusion	Relapsed disease	KRd, Kd	-Hypertension, cardiac failure, acute renal failure -Thrombotic microangiopathy -Anaemia , neutropenia -Low incidence of treatment-emergent neuropathy
Ixazomib reversible boronic acid proteasome inhibitor	Oral	Relapsed disease	IRd	-Thrombocytopenia -Gastrointestinal toxicity -Rash -Lower incidence of neuropathy when compared to bortezomib
Immunomodulatory Drugs				

Thalidomide binds to cereblon and thereby triggers proteasomal degradation of Ikaros and Aiolos, leading to direct anti-MM activity, as well as immunomodulatory and stromal-cell effects	Oral	First-line and relapsed therapy	MPT, CTD, VTD	-Peripheral neuropathy -Venous thromboembolism -Somnolence -Fatigue -Rash -Constipation -Teratogenic effects
Lenalidomide Similar MoA but with different cereblon binding affinity/properties	Oral	First-line therapy Relapsed disease	Rd, dara-Rd, VRD, maintenance after auto-SCT Rd, dara-Rd, elo-Rd, KRd, IRd	-Bone marrow suppression -Venous thromboembolism -Rash -Chronic diarrhea or constipation -Neuropathy and somnolence are rare -Increased risk of second primary malignancies -Renally excreted, dose reduction in renal impairment
Pomalidomide As for lenalidomide, but with greater activity at lower levels of cereblon	Oral	Relapsed disease	Pd; dara-Pd; elo-Pd, PCd, PVd	-Bone marrow suppression -Venous thromboembolism -Rash -Neuropathy and somnolence are rare
HDAC inhibitors				
Panobinostat Pan-deacetylase inhibitor	Oral	Relapsed disease	Pano-Vd	-Thrombocytopenia -Diarrhea -Fatigue
Monoclonal antibodies				
Elotuzumab Humanized monoclonal antibody against SLAMF7, with anti-MM activity via ADCC and	IV infusion	Relapsed disease	elo-Rd, elo-Pd	-Infusion-related reactions -Interference with response evaluation assays in patients with IgG-kappa M-protein

ADCP, and also directly activates NK cells.				
Daratumumab Fully human CD38-targeting antibody, which has classic Fc-dependent immune effector mechanisms such as CDC, ADCC, and ADCP, but also immunomodulatory effects via the elimination of CD38-positive Tregs, Bregs, and MDSCs.	IV infusion or SC administration	First-line therapy Relapsed disease	dara-VMP, dara-Rd, dara-VTD Single agent, dara-Rd, dara-Vd, dara-Pd, dara-Kd	-Infusion-related reactions -Interference with response evaluation assays in patients with IgG-kappa M-protein -Interference with blood group serological testing
Isatuximab Chimeric CD38-targeting antibody, which can directly induce apoptosis and also has classic Fc-dependent immune effector mechanisms such as ADCC and ADCP, as well as immunomodulatory effects.	IV infusion	Relapsed disease	Isa-Pd Isa-Kd	-Infusion-related reactions -Interference with response evaluation assays in patients with IgG-kappa M-protein -Interference with blood group serological testing
Antibody-drug conjugates				
Belantamab mafodotin An anti-BCMA immunoconjugate with an afucosylated, humanized anti-BCMA monoclonal antibody conjugated by a protease-resistant linker to a microtubule-disrupting drug (monomethyl auristatin F; MMAF)	IV infusion	Relapsed disease	Single agent	-Keratopathy -Thrombocytopenia
Nuclear export inhibitors				

Selinexor An orally bioavailable, selective Exportin 1 (XPO1) inhibitor.	Oral	Relapsed disease	Sd	-Nausea, anorexia, diarrhea -Hyponatremia -Thrombocytopenia -Fatigue

Abbreviations:

MPT, melphalan-prednisone-thalidomide; MPV, melphalan-prednisone-bortezomib; CTD, cyclophosphamide-thalidomide-dexamethasone; CRD, cyclophosphamide-lenalidomide-dexamethasone; VCD, bortezomib-cyclophosphamide-dexamethasone; VCP, bortezomib-cyclophosphamide-prednisone; KCD, carfilzomib-cyclophosphamide-dexamethasone; PAD, bortezomib-doxorubicin-dexamethasone; DT-PACE, dexamethasone-thalidomide-cisplatin-doxorubicin-cyclophosphamide-etoposide; VTD, bortezomib-thalidomide-dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone; Vd, bortezomib-dexamethasone; dara-VMP, bortezomib-melphalan-prednisone plus daratumumab; pano-Vd, panobinostat-bortezomib-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; Kd, carfilzomib-dexamethasone; IRd, ixazomib-lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; dara-Rd, daratumumab-lenalidomide-dexamethasone; elo-Rd, elotuzumab-lenalidomide-dexamethasone; Pd, pomalidomide-dexamethasone; dara-Pd, daratumumab-pomalidomide-dexamethasone; PVd, pomalidomide-bortezomib-dexamethasone; elo-Pd, elotuzumab-pomalidomide-dexamethasone; PCd, pomalidomide-cyclophosphamide-dexamethasone; dara-VTD, daratumumab plus bortezomib-thalidomide-dexamethasone; dara-Vd, daratumumab-bortezomib-dexamethasone; dara-Kd, daratumumab-carfilzomib-dexamethasone; Isa-Pd, isatuximab-pomalidomide-dexamethasone; Isa-Kd, isatuximab-carfilzomib-dexamethasone; Sd, selinexor-dexamethasone.

AVN , avascular necrosis; DIRA, daratumumab-specific IFE reflex assay; DTT, dithiothreitol; SPEP, serum protein electrophoresis; IFE, immunofixation electrophoresis; CrCl, creatinine clearance; TLS, tumor lysis syndrome; ESRD, end-stage renal disease; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; Treg, regulatory T-cell; Breg, regulatory B-cell; MDSC, myeloid-derived suppressor cell.

FIGURE LEGENDS

Figure 1. Cell cycle dysregulation in myeloma

Both initiating and acquired genetic events, along with other downstream effects, contribute to drive the dysregulation of cell cycle control, leading to cell proliferation and clonal growth. (adapted from figure in Pawlyn C and Morgan GJ *Nature Reviews Cancer* volume 17, pages 543–556(2017))

Figure 2. Risk-stratification and follow-up of MGUS and SMM patients

Follow-up of MGUS and SMM is based on risk of progression to symptomatic disease. (A) Recommendations for follow-up of MGUS patients are based on International Myeloma Working Group (IMWG) criteria[155] with some modifications (EMN)[53,55]. Risk of progression to MM, or other lymphoproliferative malignancies is predicted by the Mayo Clinic Risk stratification model[56]. (B) Recommendations for follow-up of SMM patients are based on IMWG criteria[155], with some modification according to risk[53]. The IMWG prognostic scoring system gives an estimate of the risk of progression[57].

Follow-up should include laboratory testing for complete blood count, creatinine, calcium, M-protein, free light-chains) and urine (Bence Jones, total protein), careful history and directed examination. Where free light-chain ratio is abnormal, with increase of the involved light-chain, NT-pro-BNP and urinary albumin should be tested to exclude AL amyloidosis. Repeat bone marrow biopsy and skeletal imaging[32] are required if symptoms or signs of progression, including abnormalities in laboratory results, develop.

*End-organ damage includes hypercalcemia, renal insufficiency , anemia , and lytic bone lesions (see Table 1).

Figure 3. Treatment algorithm for MM patients with first relapse.

Treatment at the time of first relapse is dependent on patient- and tumor-characteristics, while type and response to prior therapy are critical for selection of the next treatment regimen.

Patients with lenalidomide-refractory disease benefit from proteasome inhibitor or pomalidomide-based regimens. Patients who develop relapse without being lenalidomide-refractory, can be treated with a lenalidomide-based regimen. Retreatment with proteasome inhibitors may also be considered in patients who received PI-based first-line treatment with a treatment-free interval of >6 months. Shown are the doublet and triplet regimens, which were evaluated in large randomized phase 3 trials. Triplet regimens have a better activity profile, when compared to doublet regimens, however, frail patients may derive most benefit from a doublet regimen with a favorable toxicity profile.

Abbreviations: dara-Rd, daratumumab-lenalidomide-dexamethasone; elo-Rd, elotuzumab-lenalidomide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; IRd, ixazomib-lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; Vd, bortezomib-dexamethasone; Kd, carfilzomib-dexamethasone; dara-Vd, daratumumab-bortezomib-dexamethasone; Pano-Vd, panobinostat-bortezomib-dexamethasone; SVd, selinexor-bortezomib-dexamethasone; dara-Kd, daratumumab-carfilzomib-dexamethasone; isa-Kd, isatuximab-carfilzomib-dexamethasone; PVd, pomalidomide-bortezomib-dexamethasone; isa-Pd, isatuximab-pomalidomide-dexamethasone.

Figure 4. Systemic effects of myeloma and its treatment.
Complications of the disease and of the many treatments result in a complex symptom burden in myeloma survivors affecting several organ systems. Illustrated are some of the risks and toxicities that required careful screening for, and often coordinated management by a multi-disciplinary team.