Multiple myeloma and other plasma cell diseases

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Abbreviations

AIDS = aquired immunodeficiency syndrome
ASCT = autologous stem cell transplantation
BMI = body mass index
BMPC = bone marrow plasma cells
BMSC = bone marrow stromal cells
CDK = cyclin dependent kinase
EFS = event free survival
HCV = hepatitis C virus
HSC = hematopoietic stem cells
Ig = immunoglobulin
IL = interleukin
IMiDs = immunomodulatory drugs
KRd = carfilzomib + lenalidomide + dexamethasone
MBD = myeloma bone disease
MCP = macrophage chemoattractant protein
MGRS = monoclonal gammopathy of renal significance
MGUS = monoclonal gammopathy of undetermined significance
MIDD = monoclonal IgG deposition disease
MM = multiple myeloma
MP = melphalan + prednisone
OPG = osteoprotegerin
OS = overall survival
PC = plasma cells
PI = proteasome inhibitors
POEMS = polyneuropathy, organomegaly, endocrinopathy, myeloma protein and skin changes
RA = rheumatoid arthritis
SFLC = serum free light chains
SMM = smoldering multiple myeloma
TCR = T-cell receptor
TNF = tumor necrosis factor

TTP = time to progression

VCd = Bortezomib + cyclophosphamide + dexamethasone

VRd = Bortezomib + lenalidomide + dexamethasone

VTE = venous thromboembolism

VTd = Bortezomib + thalidomide + dexamethasone

Contents

Abstract

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This graduate thesis reviews multiple myeloma (MM), a malignant disease of plasma cells. It accounts for 1% of all cancers and is the 2nd most common hematologic malignancy after lymphoma. It is considered a disease of the elderly, with a median age of 66-70 year at diagnosis.

Monoclonal gammopathy of undetermined significance (MGUS) is premalignant condition of MM followed by smoldering multiple myeloma (SMM) and finally symptomatic MM. To differentiate the 3 conditions, the international myeloma working group has set criteria that can differentiate MGUS, SMM and MM.

Symptomatic MM is characterized by the end organ damage described by the acronym CRAB, that is, hypercalcemia, renal insufficiency, anemia and bone lesions. Beside CRAB symptoms, MM patients also suffer from infections, possible thrombosis and bleeding, all described in this graduate thesis.

MM therapy has tremendously progressed over the past decades since introduction of autologous stem cell transplantation (ASCT) and resulted in achieving deeper remission and prolonging the life span of MM patients. Multiple protocols exist regarding combinations of medications and nowadays they largely include a triple therapy with a proteasome inhibitor, immunomodulatory drug and a corticosteroid.

Key words: Multiple myeloma, monoclonal gammopathy of undetermined significance, CRAB, autologous stem cell transplantation

Sažetak

Multipli mijelom i druge bolesti plazma stanica

Dor Moritz

Ovaj diplomski rad obrađuje multipli mijelom (MM), zloćudnu bolest plazma stanica Mijelom čini 1% svih vrsta zloćudnih bolesti i druga je najčešća hematološka zloćudna bolest nakon limfoma. Smatra se bolešću starijih osoba, koja je dijagnosticirana s medijanom dobi od 66 do 70 godina.

Monoklonalna gamapatija neutvrđenog značenja (engleski **MGUS**, *Monoclonal Gammapathy of Undetermined Significance*) je premaligno stanje nakon čega slijedi a**simptomatski („šuljajući“,** engleski **„smoldering“**) mijelom (SMM) I konačno simptomatski MM. Da bi se razlikovala navedena tri stanja, međunarodna radna skupina za mijelom postavila je kriterije koji mogu razlikovati MGUS, SMM i MM.

Simptomatski MM karakterizira oštećenje ciljih organa koje uzrokuje hiperkalcijemiju, bubrežnu insuficijenciju, anemiju i koštanu leziju (CRAB simptome). Osim symptom CRAB-a, bolesnici s MM-om također mogu imati infekcije, tromboze i krvarenja, što je također opisano u ovom diplomskom radu.

Liječenje MM-a je u posljednjih nekoliko desetljeća izuzetno napredovalo uvođenjem autologne transplantacije matičnih krvotvornih stanica i rezultiralo je postizanjem duboke remisije I produljenjem životnog vijeka oboljelih od MM-a. Postoje brojni protokoli za liječenje MM-a koji danas uglavnom uključuju trostruku terapiju s inhibitorom proteasoma, imunomodulatornim lijekom i kortikosteroidom**.**

Ključne riječi: multipli mijelom, monoklonalna gamapatija neodređenog značenja, CRAB, autologna transplantacija matičnih krvotvornih stanica

1. Introduction

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. The plasma cells proliferate in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. The diagnosis of MM is often suspected because of one (or more) of the following clinical presentations:

- Bone pain with lytic lesions discovered on routine skeletal films or other imaging modalities
- An increased total serum protein concentration and/or the presence of a monoclonal protein in the serum or urine
- Systemic signs or symptoms suggestive of malignancy, such as unexplained anemia
- Hypercalcemia, which is either symptomatic or discovered incidentally
- Acute renal failure with a bland urinalysis or rarely the nephrotic syndrome due to concurrent immunoglobulin light chain (AL) amyloidosis.

It is important to distinguish MM both from other causes of the clinical presentations above and from other plasma cell dyscrasias for the purposes of prognosis and treatment. It is also important to evaluate patients suspected of having MM at the right time since a major delay in diagnosis has been associated with a negative impact on the disease course.

2. Epidemiology

Multiple myeloma accounts for 1% of all cancers and is the 2nd most common hematologic malignancy after lymphoma with an estimated 24,280 to 30,330 new cases and 12,650 deaths in 2016 [1-3]. About 99% of cases are diagnosed in people over age 40 and the median age of patients at diagnosis is approximately 66–70 years [1, 4].

MM is considered extremely rare in people less than 30 years old with a reported frequency of 0.02% to 0.3% and occurs slightly more frequently in men [5, 6]. In general, MM is not considered to be a genetic disease, however familial cases, although rare, are reported [7]. Interestingly though, it was observed that relatives of patients who had monoclonal gammopathy of undetermined significance (MGUS, premalignant condition of MM), when compared to normal controls, had a higher relative risk of developing MGUS (2.8 fold), MM (2.9 fold), Waldenström macroglobulinemia (4.0 fold), and chronic lymphocytic leukemia (2.0 fold).

MM has profound differences between races in both incidence and outcome. When compared to European Americans (EA), MGUS and MM have been observed to occur twice as frequently in African Americans (AAs), but with similar transformation rates from MGUS to MM in both races. In addition, older published studies have suggested same or even worse survival outcomes in AAs [8].

There was also found to be a positive association between obesity and having an increased risk of MM. According to a number of epidemiological studies where they measured BMI, waist circumference and hip circumference, there was found to be an elevated relative risk for having MM [9]. Few researchers have found a positive correlation between patients having RA, AIDS and HCV and MM as well [10-12].

Most importantly, in the past decade survival rates have improved significantly for the general population which is most likely due to the increasing availability

of effective therapy, namely autologous stem cell transplant (ASCT) [13,14]. For example, it has been reported that the median survival in patients with relapsed MM prior to 2000 was 12 months compared to 24 months for after 2000 [15]. Modern therapies, namely, the immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), have further contributed patients with MM to survive longer as has been observed in improvements in 5- and 10- year survival rates [14]. In another study, 5-year relative survival was found to increase from 34% in 1989–1992 to 56% in 2001–2005 periods of diagnosis[16].

3. Pathogenesis

To discuss the pathogenesis of MM, it is appropriate to firstly describe the development of B-cells into plasma cells and then, to describe the premalignant conditions that precede the development of the full malignant disease.

3.1 From B-cells into plasma cells

In the bone marrow, there are hematopoietic stem cells (HSCs) that precede all blood cells. Firstly, HSCs differentiate into multipotent progenitor cells and then into common lymphoid progenitor cells [17]. From this point, they mature into B cells through several stages in the bone marrow and then migrate through the blood to the spleen and lymph nodes (secondary lymphoid organs or SLO), which receive a constant supply of antigens through circulating lymph [18]. At the SLO, B cell acts as an antigen presenting cell (APC) and takes up offending antigens via receptor mediated endocytosis, and processes them. Pieces of the antigen are placed on MHC II molecules and presented to CD4+ T cells (T helper cells). These T cells bind to the MHC-II antigen molecule and by that causing activation of the B cell. This is a type of system safeguard; almost like a two-step security levels - first, B cells has to encounter a foreign antigen, and are then needed to be activated by T helper cells before they can differentiate into specific cells [19]. Once the B cells are stimulated by T cells, a process that usually happens in the germinal centers of SLO, the activated B cells begin to differentiate into a more specialized cells. These germinal center B cells can differentiate into memory B cells or plasma cells. The majority of them will firstly become **plasmablasts** (immature plasma cells), and after further development in the germinal centers will became **plasma cells that secrete antibodies** [20, 21].

3.2 The path to disease

Initial important events

Translocations

Early in medicine it is learnt that the majority of malignant tumors are comprised, broadly, from genetic and environmental factors. One of the most important genetic changes is chromosomal translocation. Chromosomal translocation is a chromosome abnormality caused by rearrangement of parts between nonhomologous chromosomes. A fusion between genes may be created when the translocation joins two genes that were previously separated. Broadly speaking, a chromosomal translocation between the immunoglobulin heavy chain gene (on chromosome 14, locus q32) and an oncogene (often 11q13, 4p16.3, 6p21, 16q23 and 20q11) [22] is frequently seen in patients with MM. This mutation results in dysregulation of the oncogene which becomes overexpressed and results in a proliferation of a plasma cell clone and genomic instability that leads to further mutations and translocations. The chromosome 14 abnormality is observed in about 50% of all cases of myeloma; deletion of (parts of) chromosome 13 is also observed in about 50% of cases [23].

Cyclin D

The rise of Cyclin D protein throughout the cell cycle and especially at G1 phase, causes it to bind to CDK molecule forming Cyclin-CDK complex that phosphorylate RB protein, enabling the cell to move from G1 to S phase and basically replicate. CCND is the gene behind Cyclin D protein and its upregulation causes increased expression of cyclin D, which causes excessive mitosis. There is an increased expression of CCND in virtually all MGUS and MM tumors [24, 25].

Ras Family

Ras protein family members belong to a class of proteins called small GTPase, involved in cellular signal transduction. When Ras is 'switched on' by

incoming signals, it subsequently switches on other proteins, which ultimately turn on genes involved in cell growth, differentiation and survival. Mutations in Ras genes can lead to the production of permanently activated Ras proteins. As a result, this can cause unintended and overactive signaling inside the cell, even in the absence of incoming signals. The prevalence of activating NRAS or KRAS mutations is about 15%–18% each in newly diagnosed and relapsed MM tumors [24, 26] and there's evidence that KRAS mutations provide a molecular mark to the transition of MGUS to MM [27, 28].

3.3 Monoclonal gammopathy of undetermined significance (MGUS)

It is important to discuss MGUS because it is a risk factor of developing MM. MGUS transforms into MM at the rate of 1% to 2% per year, and many cases of MM are preceded by MGUS [29]. So what is MGUS? MGUS is a condition where a monoclonal protein, an abnormal immunoglobulin, is found in the blood during a routine laboratory blood tests. This abnormal antibody is often an immunoglobulin light chain produced by large amounts by an abnormal monoclonal proliferation of plasma cells. Other names for this antibody are M protein, M spike, or paraprotein. MGUS is similar to MM but in the former, the levels of antibodies are lower [30], the number of plasma cells in the bone marrow is lower, and it does not cause CRAB symptoms. More specifically, MGUS has to fulfill the following criteria [31]:

1. A serum monoclonal paraprotein band less than 30 g/l (< 3g/dl);
2. Plasma cells less than 10% on bone marrow examination;
3. No evidence of bone lesions, anemia, hypercalcemia, or renal insufficiency related (CRAB) to the paraprotein, and
4. No evidence of another B-cell proliferative disorder.

There are three different types of MGUS, each has its own risk of progressing through an intermediate, which is a more advanced premalignant stage, to a malignant plasma cell dyscrasia or lymphoproliferative disorder [32-37].
Non-IgM MGUS (IgG, IgA, or IgD MGUS) is the most common subtype of MGUS [37, 38] and the minority of its cases will progress to the more advanced

premalignant stage smoldering multiple myeloma (SMM) and to symptomatic multiple myeloma (MM). Less frequently, these patients progress to AL amyloidosis, light chain deposition disease, or another lymphoproliferative disorder [38].

IgM MGUS accounts for approximately 15 %of MGUS cases and can progress to smoldering Waldenström macroglobulinemia (WM), to symptomatic WM as well as non-Hodgkin lymphoma (NHL) [37, 39]. Light chain MGUS (LC-MGUS) is a unique subtype of MGUS where the secreted monoclonal protein lacks the immunoglobulin heavy chain component. LC-MGUS may progress to idiopathic Bence Jones proteinuria, light chain MM, AL amyloidosis, or light chain deposition disease [33].

While only a small percentage of patients with MGUS will progress to a plasma cell malignancy or lymphoproliferative disorder, many malignant plasma cell dyscrasias are preceded by MGUS. In two large longitudinal studies, virtually all patients diagnosed with MM had MGUS prior, with 75 % having a detectible M-protein ≥8 years prior to the diagnosis of MM [29, 36]. Likewise, another large study showed many patients with AL amyloidosis had a preceding MGUS, with evidence of a monoclonal gammopathy being present in 80% at least 4 years prior and in 42% more than 11 years prior to the diagnosis of amyloidosis [40].

Prevalence of MGUS increases as the patient ages [41]; this fact has been proven countless times in epidemiological studies. In Sweden, the United States, and western France for example, approximately 1.5% of persons older than 50 years of age and 3% of the population more than 70 years of age have evidence of M protein, which indicates having MGUS, but without evidence of MM or any other related disorder [42-44]. Regarding racial differences, the prevalence of MGUS is higher in AAs than in Caucasians. For example, in the general population, 8.6% of 916 AAs had an M protein, compared with 3.6% of Caucasians in North Carolina [45].

Patients with MGUS should be monitored for the progression of the disease and for potential complications. Not all people with MGUS have the same risk

of disease progression and there's not one factor existing that can predict which MGUS patient will have a benign clinical course from one who will eventually develop a malignant plasma cell or lymphoproliferative disorder. The risk of progression to a serious disease ranges widely from 0.6 to 3.4 percent/year according to the initial value of serum monoclonal protein [38, 46-48] or from 0.25 to 2.9 percent/year according to a risk stratification model [49, 50]. The risk-stratification model is useful for predicting the risk of progression of MGUS (non-IgM and IgM) to MM or a related malignancy. It includes the following three adverse risk factors:

- Serum M-protein level ≥1.5 g/dL [38, 46-48]
- Non-IgG MGUS (ie, IgA, IgM, IgD MGUS)
- Abnormal serum free light chain (FLC) ratio (ie, ratio of kappa to lambda free light chains <0.26 or >1.65) [49, 51]

The absolute risk of disease progression over 20 years for patients with various combinations of risk factors is [49, 50]:

- 3 risk factors (high risk MGUS) – 58 %
- 2 risk factors (high-intermediate risk MGUS) – 37 %
- 1 risk factor (low-intermediate risk MGUS) – 21 %
- No risk factors (low risk MGUS) – 5 %.

Monoclonal gammopathy of renal significance (MGRS)

MGRS is a subtype of MGUS and is any MGUS disorder that has a clinically significant impact on renal function. MGRS is usually caused by the deposition of a monoclonal immunoglobulin in the kidneys, causing an injury as a result [52]. The diagnosis of MGRS is made based on the presence of following: a) the disorder needs to meet the criteria of MGUS; b) a decrease in kidney function which is evidenced by a g of <40; and c) a suspicion or confirmed biopsy of cast nephropathy, glomerulonephritis, or any other morphology indicating of clonal immunoglobulin-induced kidney injury [52, 53].

3.4 Smoldering Multiple Myeloma (SMM)

Smoldering multiple myeloma is MM but still without end-organ damage (no CRAB symptoms). Roughly speaking, it is plausible to say that SMM is intermediate in the spectrum of severity between MGUS and MM.

SMM is defined as an M-protein ≥3 g/dL or monoclonal protein in urine ≥ 500 mg/L in 24 hours and/or 10 to 60 % bone marrow plasma cells but no end-organ damage (no lytic lesions, anemia, renal disease, or hypercalcemia) that can be attributed to the underlying plasma cell disorder or other myeloma-defining events, and no amyloidosis [1].

Thus, for the diagnosis of SMM, patients should **not** have any of the following myeloma-defining events:

- End-organ damage (lytic lesions, anemia, renal disease, or hypercalcemia) that can be attributed to the underlying plasma cell disorder
- ≥60 percent clonal plasma cells in the bone marrow [54, 55]
- Involved/uninvolved free light chain (FLC) ratio of 100 or more [56-58]
- Magnetic resonance imaging (MRI) with more than one focal lesion >5 mm (involving bone or bone marrow). [59-62]

As we can understand, these more severe criteria emphasize the higher risk of progression in SMM compared with MGUS. A study found that the risk of progression of SMM was 10% per year for the first 5 years after diagnosis, 3% per year for the next 5 years, and then 1% to 2% per year for the next 10 years [63]. This relatively linear decreased risk of SMM progression with time is different from the fixed 1% per year risk in MGUS progression.

Additionally, there have been described two ways in which SMM can progress: evolving SMM, which is characterized by a steady increase of the serum M protein level and non-evolving SMM, which is characterized by a stable M protein value that abruptly increases when symptomatic multiple myeloma develops [64].

Regarding time to progression from SMM to MM, it was found that the level of serum M protein and the percentage of bone marrow plasma cells (BMPC) were associated with the risk of progression from SMM to active disease. In one experiment, patients with SMM were divided into three prognostic groups by the percentage of BMPC and level of serum M protein, where in group 1 the BMPC ≥10% and serum M protein ≥ 3 g/dL; group 2: BMPC ≥ 10% but serum M protein < 3 g/dL; group 3: serum M protein ≥3 g/dL but BMPC < 10%. The median time to progression in groups 1, 2, and 3 were 2, 8, and 19 years, respectively [65].

As we learned until now, different numbers and percentages of plasma cells in the bone marrow are accounting for different definitions: one percentage will be defined as MGUS, the other will be defined as SMM and a third one will be MM.

Another predictor of progression from SMM to MM is something that is called serum free light chain (SFLC) ratio. Also called lambda and kappa chains, light chains are proteins produced by plasma cells and link together with heavy chains to produce immunoglobulins (known as antibodies). Free light chains (FLC) refer to those that are not part of whole (intact) immunoglobulins and are present in the blood. It helps to follow, monitor and diagnose conditions where there is an increased production of light chains. Some scientists claim that SFLC is one of the single most significant factors to progression. In one study it was concluded that a high SFLC ratio ≥ 100 was a sensitive biomarker of early progression to active MM. The median TTP in the SFLC ratio≥100 was 15 months versus 55 months in the SFLC< 100 [66].

3.5 Multiple Myeloma

The role of the bone marrow microenvironment

Plasma cell (PCs) is only one type of "player" in the bone marrow (BM) micro-environment where it mutually interacts with bone marrow stromal cells (BMSC), osteoblasts, osteoclasts, lymphocytes and endothelial cells [67]. Culture of PCs in vivo for example, is only possible in the presence of BMSC [67]. The interaction of PCs with other BM elements that is thought to lead to the development of MM will be described.

Interleukin 6 (IL-6)

IL-6 is produced by macrophages, endothelial cells, fibroblasts and many other cell types as a response to IL-1 and tumor necrosis factor (TNF). Interaction between MM cell and BMSCs stimulates IL-6 secretion [68]. Originally viewed as a regulator of normal B-cell differentiation, IL-6 has shown to promote myeloma cell proliferation and protect cells from apoptosis [69]. It has a close relationship to the pathogenesis of MM and had shown the following characteristics: 1) IL-6 induces in vitro growth of myeloma cells isolated from MM patients; 2) MM cells spontaneously produce IL-6 and express the corresponding receptor; 3) treatment of MM patients with antibodies against IL-6 has shown anti-tumor effect [70-72]; 5) retinoic acid induces apoptosis in MM cells by down-regulating the expression of the IL-6 receptor [73].

Evasion from destruction

In one experiment, after co-culture with BMSCs, MM cells had increased levels of phosphorylated AKT and ERK, cyclin D2, CDK4, and Bcl-XL (factors that promote cell cycle progression) [74, 75], and decreased cleaved caspase 3 and PARP (pro-apoptotic factors) [29], which are important signaling pathways that show us the reason for increased survival in MM cells. In MM patients, dendritic cells (DCs) presented a lower expression of HLA-DR, CD40 and

CD80 antigens (which are needed in order to be recognized by the T-cell receptor (TCR)), and thus resulted in impaired activation and proliferation of T-cells compared with controls. These DCs were unable to present the specific tumor antigen to autologous T-cells, leading to the evasion of these malignant cells from destruction [76].

Osteoclast activation

Under normal conditions, there is a homeostasis between bone synthesis and bone destruction (osteolysis) via tight regulatory mechanism. This regulatory mechanism is called Receptor Activator of NF-κB Ligand (known as RANK-L) -RANK-osteoprotegerin (OPG) system [77-79]. Osteocytes express on their surface two important components: 1) the RANK-L which when associates with its receptor RANK on the surface of osteoclasts leads to their differentiation and activation, contributing to the decrease of bone matrix and to osteolysis; 2) the osteoprotegerin which attaches to RANK-L and inhibits it to interact with RANK, leading to inability to activate osteoclasts and balances bone resorption. RANK-L activity is countered also by interferon-gamma (INFγ) [78, 80-82].

In a complex molecular process, MMcells interact with BMSC via binding receptors VLA-4 and VCAM-1 [83, 84], leading to the expression RANK-L, TNF-α, and macrophage inflammatory protein 1 alpha (MIP-1α) on the surface of MM cells [85]. This leads to the dysregulation of RANK expression on osteoclast precursor cells and directly promote osteoclast formation. It is also causing the MM cells to downregulate the expression of the RANK-L decoy receptor (OPG) on osteocytes [86, 87], which contributes to osteoclastogenesis.

CD28, CD38 and PD-L1

Few receptor abnormalities are associated with the BM microenvironment that promote tumor growth and burden.

The role of CD8+ T-cells is to recognize and eliminate cells infected by intracellular pathogens [88] as well as neoplastic cells [89], and TCR identifies such cells by interacting with MHC-1 receptor presented on the surface of

antigen-presenting cells (APCs) such as DCs and macrophages/monocytes [90]. The stimulation via TCR-MHC alone is not sufficient to activate the CD8+ T cells [91-93] and a co-stimulatory signal is needed [93]. This co-stimulus is the interaction of CD28 co-receptor of the T cell and CD86 or CD80 of the APC [90, 91]. This data suggest that decreased CD28 expression as a co-receptor on T-cells can lead to malignant cells evasion from destruction; and high levels of CD8+ absent CD28 T-cell population were found both in the microenvironment and peripheral blood of patients with solid tumors and hematologic malignancies such as MM [94, 95].

CD38 is another example of a cell surface protein normally located on the surface of plasma cells (and other cell types). It was found that there are higher concentrations of CD38 on the surface of malignant plasma cells [96] and that is why it became a therapeutic target for MM; namely anti-CD38 antibodies such as daratumumab [97].

Another factor in long list of factors contributing to the pathogenesis of MM is programmed cell death ligand 1 (PD-L1) [98], a molecule expressed on the cell surface. This molecule has not been observed in normal epithelial cells or normal plasma cells, but is highly expressed in many solid tumors and MM cells [99], while its ligand PD-1 is found on a wide proportion of T-cells in MM patients. The interaction between PD-L1 and PD-1 are leading to T-cell anergy upon cellular contact, thus escaping immunosurveillance [99, 100].

Vascular endothelial growth factor (VEGF)

VEGF is the major protein involved in the formation of new blood vessels (angiogenesis) both in physiological and in pathological conditions [101, 102]. The microvessel density is estimating the degree of BM angiogenesis and was shown to be a powerful prognostic factor for survival in MM [103, 104]. Apparently, MM cells have the ability to secrete VEGF that produces its effects via its receptors VEGFR1 and VEGFR2 [105], on BMSC and endothelial cells. BMSC and endothelial cells on the other hand, produce IL-6 that are a potent growth factor for MM cells that will in turn produce VEGF and so on, in a loop-like manner [106, 107]. Apart from the stimulation of neovascularization and the increase of production of cytokines and proteolytic enzymes

contributing to neo-angiogenesis, VEGF leads to upregulation of some proto-oncogenes typically found in MM, such as V-ras, K-ras, V-raf, Src and Fos [108].

4. Clinical manifestations of MM

The International Myeloma Working Group criteria for the diagnosis of MM emphasize the importance of end-organ damage in making the diagnosis of MM [37]:

A) Clonal bone marrow plasma cells ≥10 percent or biopsy-proven bony or soft tissue plasmacytoma – Clonality needs to be proven by showing a kappa/lambda light chain restriction on flow cytometry, immunohistochemistry or immunofluorescence. The percentage of bone marrow (BM) plasma cells should be estimated from a core biopsy specimen. If there is disparity between the aspirate and core biopsy, the highest value should be used. Approximately 4 percent of patients may have fewer than 10 % BM plasma cells since marrow involvement may be focal, rather than diffuse. Repeated BM biopsy should be considered in those patients.

B) Plus one of the following:

Presence of related organ or tissue impairment (known by the acronym **CRAB**) – End-organ damage is suggested by increased plasma **C**alcium level, **R**enal insufficiency, **A**nemia, and **B**one lesions. In order to be included as diagnostic criteria, changes in these factors must be felt to be related to the underlying plasma cell proliferative disorder.

For these purposes, the following definitions are used:

•Anemia – Hemoglobin <10 g/dL (<100 g/L) or >2 g/dL (>20 g/L) below normal

•Hypercalcemia – Serum calcium >11 mg/dL (>2.75 mmol/liter). Other causes of hypercalcemia need to be excluded (for example, hyperparathyroidism).

•Renal insufficiency – Estimated or measured creatinine clearance <40 mL/min or serum creatinine >2 mg/dL (177 µmol/liter) above normal. Of these, creatinine clearance is the preferred measure of renal insufficiency because normal serum creatinine levels may vary by age, sex, and race.

Using creatinine clearance ensures that a similar level of renal dysfunction is required to define end-organ damage.

•Bone lesions – One or more osteolytic lesions ≥5 mm in size on skeletal radiography, magnetic resonance imaging (MRI), CT, or positron emission tomography (PET)/CT. In the absence of osteolytic lesions, the following are not sufficient markers of bone lesions: increased FDG uptake on PET, osteoporosis, or vertebral compression fracture. When a diagnosis is in doubt, biopsy of the bone lesion should be considered.

Manifestations of non-CRAB end-organ damage (eg, hyperviscosity, recurrent bacterial infections, AL amyloidosis, and peripheral neuropathy) are nonspecific and not diagnostic of MM.

Presence of a biomarker of malignancy (associated with near inevitable progression to end-organ damage) – ≥60 percent clonal plasma cells in the BM [58, 59]; involved/uninvolved FLC ratio of 100 or more (when involved FLC level is at least 100 mg/L) [109, 111]; or MRI with more than one focal lesion (involving bone or BM) [112-114].

4.1 Bone lesions

Lytic bone lesions related to osteoclast activation (cytokine mediated) are the hallmark of MM [115]. Bone pain, especially in the back or chest, and less commonly in the extremities, is present in approximately 60 percent of patients at the time of diagnosis [116]. The pain is usually induced by movement and does not occur at night except with change of position. Lesions within the vertebral column may lead to vertebral collapse and a decrease in the patient's height. Regarding spontaneous fractures – in one study 3049 patients suffering from malignancy-related bone disease (not only MM) were evaluated over a 21 months period, and showed that the highest incidence of spontaneous fractures were observed in MM patients (43%), as compared to breast, prostate and lung cancer [117]. Bone destruction in MM can involve any bone [115], most commonly the spine (49%), skull (35%),

pelvis (34%), ribs (33%), humerus (22%) and femur (13%). Solitary bone plasmacytomas are plasma cell masses arising from bones; the pelvis and proximal femur are common sites of solitary plasmacytomas [118]. They may affect the blood supply of the spinal cord, the vertebral column, the meninges or the nerve roots, thus leading to sensation defect (parasthesias), muscle weakness and dysfunction or even loss of bladder or bowel sphincter control. These issues are regarded as an emergency and require immediate management in order to avoid paralysis [115, 119]. MM bone disease (MBD) is assessed by skeletal x-rays of the skull, chest, spine, pelvis, humeri, and femora, although conventional radiographs are not sensitive enough to reveal small lesions and efforts are continuously made to improve MBD routine imaging. Nevertheless, about 80% of MM patients are presenting with some kind of MBD at diagnosis [120].. Death risk is increased by more than 20% in MM patients who present with fractures [120]. Nowadays, cross-sectional imaging is preferred over plain radiographs for the detection of bone involvement in patients being evaluated for suspected MM [121]. One of three modalities can be used: 1.Whole body low dose non-contrast CT scan 2. Whole body combined fluorine-18-labeled fluorodeoxyglucose PET/CT 3. Whole body MRI (or at a minimum MRI of the spine and pelvis).

4.2 Hypercalcemia

Hypercalcemia remains the most frequent metabolic complication in patients with MM, and excessive osteolysis plays a major contributory role in its pathogenesis. The normal calcium range is 2.1–2.6 mmol/L (8.8–10.7 mg/dL) with levels greater than 2.6 mmol/L defined as hypercalcemia. In one series of patients with MM, hypercalcemia was found in 28 % of them at the time of diagnosis; in 13 % of them the serum calcium was ≥11 mg/dL (2.75 mmol/liter) and required an emergent treatment [116]. The clinical presentation of hypercalcemia in patients varies depending on the level of ionized calcium. It can be life threatening, as in the case of hypercalcemic crisis [122] (that can cause oliguria, anuria, somnolence or coma) requiring immediate medical treatment to prevent death or may be

asymptomatic; patients may complain of a variety of symptoms such as anorexia, nausea, vomiting, polyuria, polydipsia, increased constipation, weakness, confusion, or stupor. Hypercalcemia can also contribute to the development of renal insufficiency [116].

4.3 Renal disease

One of the hallmarks of MM is the kidney damage caused by it. The abnormal monoclonal plasma cells produce large amount of free light chains (FLC) that ultimately accumulate and cause damage to the kidney by various mechanisms. Kidney impairment may be the first clinical manifestation of MM [123] and renal impairment at presentation should be considered a medical emergency since the recovery of renal function is associated with an increase in survival [124, 125]. The renal damage in MM can be divided into **glomerular damage** and **tubular damage**. The most common glomerular damage associated with MM is **monoclonal Ig deposition disease** (MIDD). MIDD is characterized by deposition of non-amyloid monoclonal Ig light chains (LCDD), heavy chains (monoclonal Ig heavy–chain deposition disease [HCDD]), or both (monoclonal Ig light– and heavy–chain deposition disease). LCDD is the most common manifestation of MIDD, while HCDD is a less common cause of glomerular disease [126]. LCDD and HCDD in the kidney are mainly recognized on light microscopy by the nodular sclerosing appearance of the mesangium from excess matrix deposition and light and heavy-chain deposits. The nodular appearance may be preceded by a mesangio-proliferative or membranoproliferative pattern secondary to increased PDGF-b expression [127]. IF microscopy typically reveals the deposition of a monotypical FLC in the mesangium and along glomerular and tubular basement membranes [127].

Disorders of the tubular nephron observed in patients with MM are related to the renal tubular handling of FLCs [128]. The tubular damage observed in MM is divided into proximal tubular damage and distal tubular damage, but these two entities are interconnected. In MM, the high monoclonal serum

FLCs concentration results in a burden of FLCs on the proximal tubule that overwhelms the capacity of the proximal tubular receptors to reabsorb the FLCs. As a consequence, large amounts of FLCs reach the distal tubular lumen where they interact specifically with Tamm-Horsfall proteins (THPs; also known as uromodulin), generating myeloma casts. Cast formation in the distal tubule can block glomerular flow and cause proximal tubular atrophy [129], also contributing to interstitial fibrosis [130]. Simultaneously, the massive reabsorption of monoclonal FLCs within the proximal tubules induces proximal tubule cells apoptosis and DNA degradation, resulting in critical morphologic changes, such as epithelial-to-mesenchymal transition or necrosis [131]. In addition, FLCs activate a sequence of inflammatory cascade through a number of nuclear transcription factors, which in turn induce the synthesis of proinflammatory cytokines like IL-6, macrophage chemoattractant protein-1 (MCP-1), and TNFα. As a result, the histologic pattern of the myeloma cast nephropathy consists of a chronic tubulointerstitial nephropathy with marked tubular atrophy, laminated intratubular casts, and extensive interstitial fibrosis.

4.4 Anemia

The clinical consequences of myeloma-associated anemia may significantly reduce the patient's quality of life. A normocytic, normochromic anemia (hemoglobin ≤12 g/dL) in MM is present in 73 % of patients at diagnosis and in 97 % at some time during the course of the disease [116] and is associated with poor prognosis [132]. Depending on the degree of anemia and the general clinical condition, various symptoms such as weakness, fatigue, drowsiness, depression, impaired mental function, cardiac decompensation, and respiratory distress may occur. The main reason for the MM associated anemia is due to BM infiltration by plasma cells, impairing erythropoiesis. Although its frequency increases with the progression and duration of the disease, it may occur in the absence of overt infiltration of the BM by MM cells and in spite of normal leukocyte and platelet counts, a fact that is likely happening due to decreased erythropoietin production by the kidneys (due to the kidney-induced damaged by MM) [133].

4.5 Infections

Infections are a significant cause of morbidity and a leading cause of death in MM patients [22, 134]. In a study of over 3000 MM patients, it was observed that 45% of early deaths (within 6 months) were due to infections [135]. Factors that contribute to the increased risk of infection include impaired lymphocyte function, suppression of normal plasma cell function, hypogammaglobulinemia, and chemotherapy induced neutropenia.

Regarding the latter - some small studies have described an increasing spectrum of infections in MM, possibly related to the more intensive treatment approach of recent years, suggesting that the new agents may increase the risk of infections in MM patients [136-139]. Several studies have indicated that elderly MM patients in particular are highly susceptible to infections [140].
Pneumonias and urinary tract infections account for the majority infections with Streptococcus pneumoniae, Haemophilus influenza, and Escherichia coli being the most common organisms [139].

4.6 Thrombosis

Cancer in general has been shown to increase the risk of thrombosis by 4- to 5-fold [141]. Thrombotic complications are frequently observed in patients with solid tumors, such as cancers of the pancreas, lung, stomach, breast, ovaries, and brain. Multiple myeloma is no different. In fact, recent studies suggest that patients with hematological malignancies have a similar or even higher risk of venous thromboembolism (VTE) than patients with solid tumors, with the highest risk found in patients with MM, acute leukemia and CNS lymphoma [142]. It has been known that patients with MM have an increased risk of VTE for more than four decades [143]. The greatest risk was observed during the first year following diagnosis; in one study for example, the risk for VTE was found to be 7.5-fold after 1 year of follow-up and 4.1-fold after 10 years [144]. Besides VTE, the risk for arterial thrombosis (myocardial infarction, transient ischemic attack, ischemic stroke, and angina) was also significantly increased

compared with the controls, in a different study [145]. The proposed mechanisms contributing to thrombosis in MM are: **1**. an increase in von Willebrand factor and factor VIII expression have been found, and were associated with a more advanced stage of disease, even before the start of treatment [146]. **2**. A higher incidence of acquired activated protein C resistance has been observed in MM patients, which disappeared during therapy and was associated with an increased risk of VTE [147]. **3**. The over production of paraproteins has been suggested to increased blood viscosity, formation of antibodies that are procoagulable, and interference with fibrin meshwork formation. **4**. The high levels of the inflammatory cytokines associated with the chronic inflammation and **5**. The observed excess risk for both arterial and venous thrombosis in MM patients is most likely due to involvement of platelet activation [148, 149]. Furthermore, many patients with MM have impaired mobitity due to bone lesions, and several drugs used to treat MM increase prothrombotic risk.

4.7 Bleeding

Impaired primary hemostasis (platelet plug formation), characterized by prolonged bleeding time, has been frequently shown in patients with MM and is associated with clinically overt bleeding [150, 151]. It's important to mention that these cases have normal platelet count and when MM patients do present with thrombocytopenia it has been shown as a prognostic factor of shorter survival, reflecting an advanced stage of disease with greater marrow infiltration and a higher bleeding risk [116]. In acquired von Willebrand syndrome (AVWS), there is a formation of immune complexes by specific or nonspecific autoantibodies that either neutralize VWF activity or accelerate its clearance. Absorption of VWF onto the surface of malignant cell clones that aberrantly expressing VWF receptors, and proteolytic degradation due to the presence of circulating proteases have also been proposed mechanisms [150, 151] These abnormalities result in loss of circulating high molecular weight (HMW) von Willebrand multimers [152, 153]. Another coagulation abnormalities are also associated with MM, such as prolonged thrombin time (almost always

asymptomatic and is due to monoclonal protein interference with fibrin clot formation) [150, 154]. In some cases of MM complicated by severe bleeding, paraproteins with specificity for thrombin and factor VIII [150] have been identified. Both solid tumors and MM have been associated with cases of acquired hyperfibrinolysis due to excess release of tissue plasminogen activator or urokinase-type plasminogen activator [155] and circulating heparin-like anticoagulants [156].

5. Therapy

Multiple protocols and guidelines have been used for the treatment of newly diagnosed MM, both in patients who are candidates for autologous hematopoietic stem cell transplantation (ASCT) and in those who are ineligible for ASCT. It will be described basic approach to treatment of MM patients and some of the most used protocols.

Before 2000, the median survival of patients with newly diagnosed MM was approximately 2.5 years. First-generation novel agents, namely bortezomib, thalidomide, and later lenalidomide, and the introduction of ASCT have substantially improved overall survival (OS), which currently ranges from 5 to 7 years, or even more [157].

Considerations

Risk stratification

Patients diagnosed with MM are graded or "risk stratified" based on the results of fluorescence in situ hybridization (FISH) for specific translocations and certain other mutations. This risk stratification helps to determine patients' prognosis and more importantly, dictates treatment choice. Patients can be classified into high-risk MM and standard-risk MM [37, 158]:

High-risk MM – at least one of the following clinical or pathologic criteria is needed for a patient to be considered to have high-risk MM:

• t (4; 14), t (14; 16), t (14; 20), del17p13, or gain 1q by FISH.

• Lactate dehydrogenase (LDH) levels ≥2 times the institutional upper limit of normal.

• Features of primary plasma cell leukemia (defined by either ≥2000 plasma cells/microL of peripheral blood or ≥20 percent on a manual differential count).

Standard-risk MM – refers to patients who lack all of the high-risk abnormalities described above. This includes patients with trisomies, t(11;14), and t(6;14).

Transplant eligibility

Following diagnosis and risk stratification, all patients are assessed to determine eligibility for ASCT. When compared with chemotherapy alone, ASCT appears to prolong both event-free survival and OS [159]. Stem cell collection should occur early in the treatment course for all eligible patients regardless of whether the plan is for ASCT to be incorporated into the initial treatment or postponed until the time of first relapse. The initial chemotherapy given to patients who are candidates for ASCT should limit agents that may impair stem cell collection or damage stem cells. In general, treatment of MM should be divided in 3 parts: induction, consolidation and maintenance therapy.

General eligibility requirements: Eligibility for ASCT in MM varies across countries and institutions. In most European countries, transplantation for MM is offered primarily to patients younger than 65 years of age. In the United States (US), a strict age limit is not used. Instead, decisions are made on a case-by-case basis based on "physiologic age" and vary across institutions. In most centers in the US, patients with one or more of the following factors are usually not considered eligible for ASCT in MM: age >77 years, cirrhosis of the liver, Eastern Cooperative Oncology Group (ECOG) performance status 3 or 4, New York Heart Association (NYHA) functional status Class III or IV.
Three-drug regimens discussed below are the mainstay of initial therapy for most patients with MM:

Bortezomib, lenalidomide, dexamethasone (VRd)

The combination of bortezomib, lenalidomide, and dexamethasone (VRd) is one of the preferred treatment options for MM. VRd has shown tolerability and efficacy in prospective phase 2 studies [160-162]. In addition, initial results from a phase 3 trial suggest that VRd improves survival over that seen with lenalidomide plus dexamethasone (Rd), although it comes with increased toxicity [163]. Major toxicities of VRd include peripheral neuropathy, transient cytopenias, fatigue, and gastrointestinal distress. Thromboprophylaxis and antiviral prophylaxis are thus needed. Lenalidomide is teratogenic and there are emerging concerns regarding an increased risk of second primary

malignancy. Moreover, patients with renal insufficiency experience more neutropenia with the use of lenalidomide [164].

Bortezomib, cyclophosphamide, dexamethasone (VCd)

The combination of bortezomib, cyclophosphamide, and dexamethasone (VCd) has demonstrated tolerability and efficacy in the management of patients with newly diagnosed MM. At this time, VCd is a reasonable alternative if VRd is not available and in patients presenting with acute renal failure.

Bortezomib, thalidomide, dexamethasone (VTd) — The combination of bortezomib, thalidomide, and dexamethasone (VTd) is a reasonable alternative if VRd is not available, and in patients presenting with acute renal failure. In these circumstances, VTd and VCd are the two main options, and the choice between the two is based on experience with the regimen and drug availability.

ASCT eligible

Patients with MM who are candidates for ASCT, usually receive four cycles of induction therapy and if achieve good response, adequate numbers of autologous HSCs are then collected and stored.

High-dose melphalan (an alkylating agent) at a dose of 200 mg/m^2 (with dose reductions based on age and renal function) followed by ASCT is considered the standard of care for patients with MM who are eligible for ASCT. After ASCT patient can receive consolidation therapy and maintenance treatment.

ASCT ineligible

For patients with high-risk MM who are **not** candidates for ASCT, the preferred initial treatment (if available) is with bortezomib, lenalidomide, and dexamethasone (VRd) [165, 166]. Bortezomib, cyclophosphamide, and dexamethasone (VCd) is an acceptable alternative for patients at higher risk of complications with lenalidomide (eg, acute renal failure, increased thromboembolic risk) and for those in countries in which lenalidomide is not approved for initial therapy. After 8 to 12 cycles of initial therapy, bortezomib is offered as a maintenance therapy until progression.

MP, MPT and MPV

Melphalan combined with prednisone (MP) has been the historical treatment of choice for a large proportion of elderly MM patients ineligible for ASCT, and is still the backbone of new regimens that include the new era of novel agents. Once the effectivity of thalidomide was noted against relapsed/refractory myeloma, the drug was then moved up to the first line, given with MP, a combination known as MPT [167]. In the first ever two published phase III studies (GIMEMA and IFM 99–06), the superiority of MPT over MP was clearly demonstrated on the basis of response, including complete response (CR), and progression-free survival [168-170]. A later study showed similar results - the addition of thalidomide to MP resulted in a significant advantage in terms of response rate and time to progression compared with MP [201].

As written before, introduction of proteasome inhibitor bortezomib has expanded treatment options in MM and has significantly improved the outcomes for patients with relapsed/refractory MM [172, 173]. The drug was also shown to be synergistic in vitro with a wide range of cytotoxic agents, including melphalan [174]. In addition, the combination of bortezomib and melphalan was effective in a phase I/II trial [175]. Based on these promising results, bortezomib was incorporated into the MP regimen (MPV) for the treatment of elderly patients with MM [176].

Newer drugs in the treatment of MM

Pomalidomide

Pomalidomide is a second-generation immunomodulatory drug with a structure similar to thalidomide and lenalidomide. Pomalidomide exerts its antitumor activity by anti-proliferative and anti-pro-apoptotic effects on plasma cells, by bone marrow microenvironment modulation (anti-angiogenic and anti-inflammatory effects) and by immunomodulation (increase in T and NK cell activity, suppression of regulatory T cells) [177-181].

Elotuzumab

Elotuzumab is a humanized monoclonal IgG1 antibody directed against human CS1 (also known as SLAMF7), a cell surface glycoprotein highly expressed on MM cells, and at a lower level on normal plasma cells, NK cells and other T-cells [182]. CS1 mediates the adhesion of MM cells to the bone marrow stromal cells, granting their proliferation and preventing apoptosis [183]. By binding CS1, elotuzumab inhibits the stimulatory effects of the bone marrow on MM cells; furthermore, it exerts anti-MM activity via antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by NK cells [182].

Daratumumab

Daratumumab is a human IgG1 monoclonal antibody targeting a specific epitope of CD38 on the surface of MM cells [184]. It provides its anti-myeloma effect through the activation of complement-dependent cytotoxicity (CDC), ADCC and antibody-dependent cellular phagocytosis (ADCP); furthermore, daratumumab is able to induce direct apoptosis of MM cells and modulation of the enzymatic activity of CD38 [175, 184-187]. This drug was approved in November 2015 for patients whose disease had failed at least three prior therapies including an immunomodulator and a proteasome inhibitor [188]. Clinical trials have demonstrated the beneficial results upon addition of daratumumab to lenalidomide/dexamethasone or bortezomib/dexamethasone regimens. A study of 18 random clinical trials (RCTs) concluded that daratumumab + lenalidomide + dexamethasone were ranked first among other regimens in terms of activity, efficacy, and tolerability and that the combination lowered the risk of disease progression or death by 87% compared to 81% for bortezomib + dexamethasone and 63% for lenalidomide + dexamethasone [189-192].

Ixazomib

Ixazomib is a peptide boronic acid proteasome inhibitor that is used in the maintenance treatment for MM, administered orally, and has a chemical structure and pharmacologic properties that are distinct from those of bortezomib [193, 194]. Ixazomib was shown to have synergy with lenalidomide in preclinical studies [195]. Hence, ixazomib is used in combination with

lenalidomide and dexamethasone for the treatment of multiple myeloma in adults after at least one prior therapy. In one study [196, 197], ixazomib increased the median time of progression-free survival (PFS) from 14.7 months (in the placebo + lenalidomide+ dexamethasone) to 20.6 months (under ixazomib+ lenalidomide+ dexamethasone). 11.7% of patients in the ixazomib group had a CRto the treatment, versus 6.6% in the placebo group.

Carfilzomib

Carfilzomib is a second generation selective proteasome inhibitor that was approved for treatment of relapsed and refractory multiple myeloma. Carfilzomib is highly selective, irreversible epoxy-ketone molecule that targets chymotrypsin like activity of 20S proteasome leading to cellular apoptosis which is particularly beneficial in malignant cells. Prospective trials have demonstrated response rates of 40 to 50 percent on bortezomib-naïve cases and 15 to 20 percent in bortezomib-refractory cases [198, 199]. Higher response rates have been seen with combination therapy, such as carfilzomib, lenalidomide, dexamethasone (KRd).

Nivolumab, Pembrolizumab and Durvalumab – checkpoint inhibitors

Two anti-PD1 monoclonal antibodies (MoABs), nivolumab and pembrolizumab, and the anti-PDL1, durvalumab, are currently under investigation in MM patients [200]. Recently, the interaction between the tumor and the immune system has become a highly relevant clinical matter. Evidence has emerged that tumor cells may impair the immune host system control through different pathways, such as the T-lymphocyte associated protein 4 (CTLA-4) and programmed-death 1 (PD-1), blocking immune activity by expressing the ligands of immune checkpoint receptors. Thus, as checkpoint inhibitors, these MoAbs are directed against ligands and their involved receptors and allow the reversal of tumor-induced down-regulation of T-cells and the enhancement of the immune response against neoplastic cells [200].

Supportive and symptomatic treatment

Hypercalcemia

Hypercalcemia is present in large percentage of patients with myeloma at the time of diagnosis and may require emergent treatment [201]. Patients with hypercalcemia may be asymptomatic or complain of a variety of symptoms such as anorexia, nausea, vomiting, polyuria, polydipsia, increased constipation, weakness, confusion, or stupor. Hypercalcemia can also contribute to the development of renal insufficiency. Hydration that includes isotonic saline, plus dexamethasone is effective in most cases of mild hypercalcemia (serum calcium <12 mg/dL). In moderate to severe hypercalcemia (serum calcium >12 mg/dL), treatment includes hydration, corticosteroids, and a bisphosphonate such as zoledronic acid or pamidronate. Extremely severe hypercalcemia (eg, >18 mg/dL) may require hemodialysis in addition to the methods outlined above [201].

Infections

As mentioned prior, patients with MM are at increased risk for infections. The rate of infections is the highest in the first three to four months of induction therapy and in the setting of relapsed disease [202, 203]. Preventative measures that may decrease the rate of infection among patients with MM include the use of vaccines, prophylactic antibiotics or antivirals, and intravenous immunoglobulins.

Patients with MM should have yearly influenza vaccines and a single pneumococcal vaccine at the time of diagnosis. Although the antibody response is reduced in many MM patients [204-206], an individual may have a suboptimal response and still gain a benefit. A routine antibiotic prophylaxis with either a fluoroquinolone (eg, levofloxacin 500 mg daily) or trimethoprim-sulfamethoxazole (TMP-SMX) (eg, 80/400 mg once daily or 160/400 mg every other day) during the first three to four months of chemotherapy have shown to be beneficial. TMP-SMX may increase risk of serious skin toxicity with immunomodulatory agents. In addition, for all patients receiving bortezomib, antiviral prophylaxis is usually given (eg, acyclovir 400 mg twice daily or

valacyclovir 500 mg once daily) because of the increased risk of herpes zoster (varicella zoster reactivation) with this agent [207, 208].

Skeletal lesions

Skeletal lesions can result in bone pain, pathologic fractures, and spinal cord compression. All patients with MM should be encouraged to be as active as possible in order to maintain bone density while avoiding activities with an excessive risk of trauma [209]. Patients with one or more lesions on bone imaging and those with osteopenia should be given osteoclast inhibitors (eg, bisphosphonate therapy), which significantly reduces the number of skeletal events (eg, pathologic fracture, irradiation of or surgery on bone, and spinal cord compression) [210-212]. The choice among agents is principally made based on the patient's renal function, physician experience, and side effect profiles. There are limited data comparing specific bisphosphonate agents with each other, but those that exist have not found any one intravenously administered bisphosphonate to be more efficacious [212, 213]. Examples of bisphosphonates include Pamidronate, Clodronate and Zoledronic acid. An indirect comparison (network) meta-analysis, performed as part of a 2012 Cochrane systematic review evaluating data from 4766 patients, did not find any particular type of bisphosphonate to be superior to another [214].

Thrombosis

In most patients and when there is no contraindication, thrombo-prophylaxis is started at the time of diagnosis and continued until evident VTE risk factors such as prothrombotic chemotherapy or immobility resolve [215]. The International Myeloma Working Group suggests using risk-based stratification in order to make strategies for thrombo-prophylaxis based on of the patient’s underlying likelihood of having VTE using individual, MM, and therapy-related risk factors [216]. Aspirin, prophylactic dose low-molecular-weight heparin (LMWH), and low target INR warfarin seem to be as effective in reducing the risk of VTE, except in elderly patients where warfarin may be less effective than LMWH [217]. It is important to remember that the use of any of these drugs will reduce, but will not eliminate the risk of thrombosis completely.

Approximately 5–8% of patients still develop thrombosis despite prophylaxis (215, 217, 218).

6. Other plasma cell dyscrasias

6.1 Plasma cell leukemia

Plasma cell leukemia (PCL) is a rare variant of MM that presents either as a progression of previously diagnosed MM (ie, secondary PCL) or as the initial manifestation of disease (ie, primary PCL). Historically, the majority of cases have been primary PCL (60 to 70 %), although the incidence of secondary PCL may be increasing, presumably due to the longer survival of MM patients, such that the distribution of disease evenly split [219, 220].

PCL occurs in all races and all geographic locations. The incidence of PCL in Europe is approximately 4 cases per 10,000,000 persons per year [221]. As with multiple myeloma, PCL is more common in AAs than in Caucasians [222].

Presenting signs and symptoms can include those seen in MM (eg, renal dysfunction, hypercalcemia, lytic bone lesions, bone pain, anemia) and in other leukemias (eg, leukocytosis, anemia, thrombocytopenia, infections, hepatomegaly, splenomegaly [223].

The diagnosis of PCL is based on an evaluation of the peripheral blood smear, BM aspiration and biopsy, and protein electrophoresis. The diagnosis is confirmed when a monoclonal population of PCs is present in the peripheral blood with an absolute PC count exceeding 2000/microL or 20 percent of the peripheral blood white cells [224-226]. Significant involvement of the liver or pleural effusions with positive cytology for malignant PCs usually suggests PCL.

The prognosis of PCL is poor. Historically, the median survival was only 6 to 11 months, with up to 28 percent dying within the first month after diagnosis [219, 222, 224, 227]. Survival was even shorter (two to seven months) when PCL (secondary) occurred in the context of refractory or relapsed MM [219]. It is likely that the reasons for poor outcome in PCL is related to the high proliferative rate and the fact that the malignant cells often have multiple cytogenetic abnormalities that are known to be associated with rapidly progressive, or high risk, MM.

6.2 Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma, is a type of cancer affecting lymphoplasmacytoid cells. WM is characterized by having high levels of a circulating antibody, immunoglobulin M (IgM), which is made and secreted by the WBCs cells involved in the disease. WM is considered "indolent lymphoma" (tends to grow and spread slowly) and a type of lymphoproliferative disorder which shares clinical characteristics with the indolent non-Hodgkin lymphomas [228]. Similar to other plasma cell dyscrasias that, for example, lead to MM, WM is commonly preceded by two clinically asymptomatic but progressively more pre-malignant phases, IgM monoclonal gammopathy of undetermined significance (i.e. IgM MGUS) and smoldering Waldenström's macroglobulinemia. The spectrum of WM dysplasias differs from other spectrums of plasma cell dyscrasias in that it involves not only aberrant plasma cells but also aberrant lymphoplasmacytoid cells and that it involves IgM while other plasma dyscrasias involve other antibody isoforms [229, 230].

Waldenström's macroglobulinemia is characterized by an uncontrolled clonal proliferation of terminally differentiated B lymphocytes. The most common mutations, based on whole-genome sequencing, are a somatic mutation in MYD88 (90% of patients) and a somatic mutation in CXCR4 (27% of patients) [231]. There is a two- to threefold increased risk of WM in people with a personal history of autoimmune diseases with autoantibodies, and a particularly elevated risk associated with conditions such as liver inflammation, human immunodeficiency virus, and rickettsiosis [232]. There are genetic factors, with first-degree relatives of WM patients shown to have a highly increased risk of also developing the disease [233]. There is also evidence to suggest that environmental factors, including exposure to farming, pesticides, wood dust, and organic solvents, may influence the development of WM [234].

Signs and symptoms of WM include weakness, fatigue, weight loss, and chronic oozing of blood from the nose and gums [235]. Peripheral neuropathy occurs in 10% of patients. Enlargement of the lymph nodes, spleen, and/or

liver are present in 30–40% of cases [236]. Other possible signs and symptoms include blurring or loss of vision, headache, and (rarely) stroke or coma.

6.3 Amyloidosis

Amyloidosis is a group of diseases in which abnormal proteins, known as amyloid fibrils, build up in tissues [237]. Symptoms depend on the type and are often variable [238]. They may include diarrhea, weight loss, feeling tired, enlargement of the tongue, bleeding, numbness, feeling faint with standing, swelling of the legs, or enlargement of the spleen [238].

There are about 30 different types of amyloidosis, each due to a specific protein misfolding [239]. Some are genetic while others are acquired [240]. They are grouped into localized and systemic forms [238]. The four most common types of systemic disease are light chain (AL), inflammation (AA), dialysis ($A\beta_2M$), and hereditary and old age (ATTR) [238].

Diagnosis may be suspected when protein is found in the urine, organ enlargement is present, or problems are found with multiple peripheral nerves and it is unclear why [238]. Diagnosis is confirmed by tissue biopsy [238]. Due to its variable presentation, the diagnosis of amyloidosis can often take long time to reach [240].

AL amyloidosis occurs in about 3–13 million people per year [238]. The usual age of onset is 55 to 60 years old [238]. Without treatment, life expectancy is between six months and four years [238]. In the developed world about 1 per 1,000 people die from amyloidosis [240].

The clinical presentation of amyloidosis is wide and depends on the site of amyloid accumulation. The kidney and heart are the most common organs involved.

Amyloid deposition in the kidneys for example, can cause nephrotic syndrome, which results from damage to the glomerulus [241]. Amyloid deposition in the heart can cause both diastolic and systolic heart failure. EKG changes may be present, showing low voltage and conduction abnormalities like atrioventricular block or sinus node dysfunction. On echocardiography, the heart shows a restrictive filling pattern, with normal to mildly reduced

systolic function [241]. Other signs of amyloidosis are hepatomegaly, neuropathy, macroglossia, carpal tunnel syndrome and periorbital purpura.
Treatment depends on the type of amyloidosis that is present. Treatment with high dose melphalan, followed by stem cell transplantation has shown promising results and is recommended for stage I and II AL amyloidosis [242]. However, only 20–25% of people are eligible for stem cell transplantation. Chemotherapy and steroids, with melphalan plus dexamethasone, is mainstay treatment in AL patients not eligible for transplant [242].

6.4 POEMS syndrome

POEMS syndrome is a rare paraneoplastic syndrome caused by a clone of abnormal plasma cells. The name POEMS is an acronym for some of the disease's major signs and symptoms [243] (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes); PEP is used as well [244] (polyneuropathy, endocrinopathy, plasma cell dyscrasia).
The signs and symptoms of POEMS syndrome are variable and are usually due to the mass effects caused by the invasion and destruction of tissues by the neoplastic cells. This often leads to long delays (e.g. 13–18 months) between the onset of initial symptoms and diagnosis [245, 246].
POEMS syndrome typically begins in middle age – the average age at onset is 50 – and affects up to twice as many men as women [243].
Regarding the pathogenesis, the exact mechanism behind its development, remains unclear. Overproduction of the monoclonal protein and VEGF may underlie some, but probably will not explain all, of the multi-organ features of the disease [247]. It is suggested that various other cytokines produced by the clonal plasma cells, presumably working in collaboration with each other as well as with VEGF and the monoclonal proteins, cause many of the features of POEMS syndrome [248]. The other cytokines detected in, and suspected of contributing to, POEMS syndrome include interleukin 1β, interleukin 6, and TNFα [249].
Treatment depends on whether there is a local or systemic spread of the clonal plasma cells. Patients with one or two plasmacytoma bone lesions and

no clonal PCs in their BM biopsy specimens are treated by surgical removal or radiotherapy of their tumors [250] Patients with >2 plasmacytoma bone lesions and/or increases in BM clonal PCs are treated with a low-dose or high-dose chemotherapy regimen, like a corticosteroid such as dexamethasone plus an alkylating agents such as melphalan [250].

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