HNHCP
Haematology Nurses & Healthcare Professionals Group

Haematology Nurses and Healthcare Professionals (HNHCP)

Multiple Myeloma Learning Program

A Resource for Healthcare Professionals

Dear Colleagues,

We are very pleased to present the second edition of "An Introduction to Multiple Myeloma: A Resource for Healthcare Professionals" by the Haematology Nurses and Healthcare Professionals Group.

A faculty of haematology/oncology nurses, haematologists and oncologists, and patient advocates collectively developed this program dedicated to educating people on multiple myeloma.

This program includes issues relevant to the care of patients with multiple myeloma and their families from the perspective of the multidisciplinary team. Nurses, other associated healthcare professionals and patient organisations play an important role in this process and the group is delighted to share with you the latest information and recommendations on the long-term management of patients' needs.

While no sponsorship or educational grants were provided in producing this second edition the names of the sponsors of the first edition published remain on the cover in acknowledgement of their support in producing this educational resource

On behalf of the Haematology Nurses and Healthcare Professionals group that developed this resource, we hope that the Multiple Myeloma educational resource will be of value in the care of patients with multiple myeloma.

Yours sincerely,

Erik Aerts

President

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The Multiple Myeloma Tutorial is also available online at

www.hemcare.org

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Quick Facts

- Multiple myeloma is an incurable malignant disease that originates in the plasma cells. Plasma cells are at the end of the B cell line and are mature B lymphocytes.
- B lymphocytes are a type of cell in the immune system. They mature into plasma cells in the bone marrow. Abnormalities within the bone marrow result in uncontrolled growth of clonal plasma cells, a hallmark of myeloma. Myeloma is typically preceded by an asymptomatic, premalignant phase. Depending on the extent to which the bone marrow is affected and monoclonal proteins appear, these are referred to as monoclonal gammopathy of undetermined significance (MGUS) or smouldering multiple myeloma (SMM).
- Through innate (non-specific, natural or intrinsic) and acquired (adaptive) immunity, the immune system recognises and eliminates pathogens.
- The likelihood of developing myeloma increases significantly with age. The median age at onset is 70 years. Diseases in young people under 40 years of age are very rare. The peak age is between 85 and 89 years.
- Determining molecular subgroups of myeloma is a valuable basis for treatment and can lead to improved treatment outcomes.

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Understanding Multiple Myeloma

Multiple myeloma, or myeloma, is described as an increase in clonal altered plasma cells, characterized by plasmacytosis in bone marrow, production of monoclonal proteins, osteolytic bone lesions renal disease, anemia, hypercalcemia and immunodeficiency (Noonan 2021). The first known case report of myeloma dates back to 1844. At that time, the displacement of the bone marrow by a red substance was discovered, which later led to the identification of the Bence Jones protein in the urine of myeloma patients.

The development of myeloma is a complex multistep process characterised by early and late genetic changes in the tumor cell, as well as unique supportive conditions within the bone marrow microenvironment (Abramson 2018; Rajkumar 2016). Active myeloma arises from a premalignant phase known as monoclonal gammopathy of undetermined significance (MGUS), which is associated with the presence of monoclonal immunoglobulins detected in blood or urine. Smoldering multiple myeloma can also transform into active disease [refer to Module 2 for detailed information on disease phases]. Although myeloma is incurable, survival has improved largely due to advances in drug therapies, with novel drug classes now available as routine care (Costa 2017).

Overview of the immune system and immune responses

The primary function of the immune system is to protect the body against disease-causing microorganisms. These can be viruses, bacteria or fungi, but also protozoa and parasites, infectious microbes or harmless environmental substances such as pollen or food. The immune system distinguishes the body's own substances from those that are foreign to the body. If substances are recognised as foreign, they trigger an immune response.

The immune system uses two mechanisms to recognise and eliminate pathogens:

- Innate immunity (also known as non-specific, natural, or intrinsic immunity): it includes more primitive elements of the immune system, including macrophages, natural killer cells (NK) and antigen presenting cells (APC)
- Acquired immunity (or adaptive immunity): it includes T and B lymphocytes

Innate immunity

The innate immune system is the body's first line of defence and is activated immediately upon detecting the intrusion of a pathogen. This reaction is a non-specific mechanism that is not dependent on an antigen. However, it is also unable to recognise the same pathogen if it enters the body a second time.

The primary function of the innate immune system is to send immune cells to infected or inflamed sites through the production of cytokines (proteins involved in communication between cells). There are several types of cytokines that are important for the growth, activation and function of immune cells.

Cytokine types
Colony Stimulating Factors (CSF): important for cell development and differentiation
Interferons: necessary for the activation of immune cells. Type I interferons mediate antiviral immune responses; Type II interferons are important for antibacterial responses
Interleukins: provide context-specific cues with activating or inhibitory responses
Chemokines: are produced at specific sites in the body or directly at the site of infection to attract immune cells. Different chemokines attract different immune cells to the infected site
Tumour Necrosis Factor (TNF): Family of cytokines that stimulates the growth of immune cells and their activation; important for the activation of anti-inflammatory reactions

The production of cytokines leads to the release of antibodies and other proteins, which in turn set in motion a biochemical cascade designed to identify and label (opsonize) foreign antibodies. This then makes them susceptible to phagocytosis (Warrington 2011).

Innate immunity protection includes both cells of haematopoietic and non-haematopoietic origin. Haematopoietic cells include macrophages, dendritic cells,

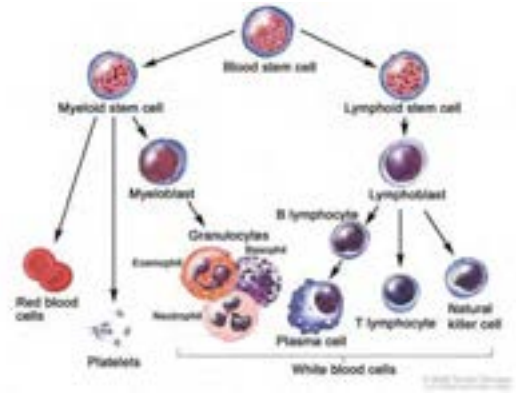

Figure 1. Development of blood cells. A stem cell goes through several stages before becoming either a red blood cell, a white blood cell, or a platelet. In multiple myeloma, mutations deregulate the development of plasma cells, causing them to spread abnormally in the bone marrow.

mast cells, neutrophils, eosinophils, natural killer (NK) cells, and natural T-killer cells (**Table 1, Figure 1**) (Turvey 2010). **Non-haematopoietic cells include epithelial cells of the skin, airways, and gastrointestinal tract.**

Acquired immunity

Adaptive or acquired immunity, in contrast to innate immunity, is a slower response to pathogens but produces long-lived memory cells that continue to exist in a dormant state until re-exposure to the pathogen occurs. Acquired immunity develops when innate immunity is inefficient in eliminating pathogens and infection exists (Warrington 2011). The primary functions of acquired immunity are:

- Recognizing specific, "not self" antigens
- Generate pathogen-specific immunological effects to eliminate a specific pathogen or pathogen-infected cells
- develop immune memory to eliminate specific pathogens (Bonilla 2010)

Some of the cells of the adaptive immune system are: T and B cells (or lymphocytes) (**Table 1, Figure 2**). T cells originate from haematopoietic stem cells in the bone marrow and mature in the thymus. They stimulate cellular immune responses. The main role of T cells in the immune response is to detect and destroy infected cells. T cells have a unique antigen-binding receptor on their membrane known as the TCR (T cell receptor). It requires activation by antigen-presenting cells (APCs), in order to be able to recognize a specific antigen. APCs are found in the epithelium of the skin, digestive tract, and airways. APCs are essential to recognise specific antigens.

The surface of APCs have major histocompatibility complexes (MHC). MHC (or human leukocyte antigens [HLA]) proteins have two general functions:

- MHC proteins act as carriers to display antigens on the cell surface. MHC type I proteins are essential to deliver viral antigens and are found in almost all cell types except red blood cells. MHC type II proteins are important for delivering antigens to helper T cells (also known as CD4 cells).
- MHC proteins also indicate whether a cell is a host cell or a foreign cell. In organ transplants, MHC proteins are matched to reduce the risk of rejection.

T cells are activated when they encounter an antigen-loaded APC presenting their antigen fragments bound to MHC molecules (Warrington 2011). Once activated, the T cell secretes cytokines, which in turn stimulates other T cells to differentiate into cytotoxic T or T helper cells. The main role of T cells is to recognise and destroy virus infected cells, intracellular bacteria or intracellular parasites (Chaplin 2010).

B cells develop from haematopoietic stem cells in the bone marrow. Once mature, they exit the bone marrow and form a unique antigen-binding receptor on their membrane (Warrington 2011). Around 1 % of B cells develop into plasma cells; an activated B cell can generate up to 4,000 plasma cells. B-cell growth and differentiation towards antibody-secreting plasma cells is activated by foreign antibodies. B cells also help with activation, anergy (disabling T cell responses after encountering an antigen), differentiation, and T cell proliferation (Noonan 2015). Activated B lymphocytes produce anti-inflammatory cytokines such as IL-1 and IL-6, granulocyte-macrophage colony-stimulating factor and tumour necrosis factor (TNF).

Humoral and cellular immunity

As mentioned above, the main function of B cells is the production of antibodies against foreign antigens: humoral or antibody-mediated immunity is that branch of acquired immunity mediated by B cells in the production of antibodies. T lymphocytes and other cells, such as dendritic cells, mediate the production of antibodies by plasma cells that have evolved from B cells. Antibodies found in serum and mucosal fluids recognize extracellular microbial antigens and neutralize and eliminate microbes. B cells produce five types of antibodies: immunoglobulin

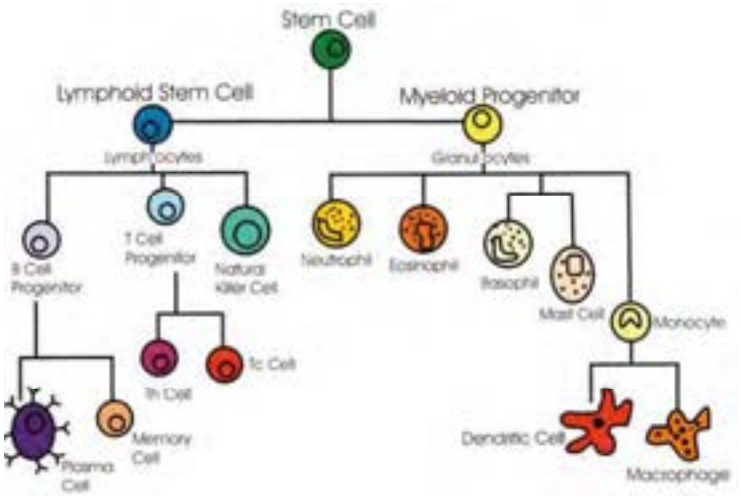

Figure 2. Cells of the immune system. All cells are derived from a multipotent stem cell in the bone marrow.

A (IgA), IgD, IgE, IgG and IgM. Each of these antibodies has different biological functions and each recognizes and neutralizes specific pathogens (Warrington 2011).

Cell-mediated immunity does not involve antibodies, but rather provides protection through:

- the activation of antigen-specific cytotoxic T cells
- the activation of macrophages and natural killer cells
- the stimulation of cytokine production, which mediates the immune response

Cell-mediated immunity is the main function of T lymphocytes, protecting the body against microbes such as viruses (Noonan 2015).

The innate and adaptive immune systems are not separate mechanisms, but rather synergistic processes; many acquired immune responses are based on innate immunity. For example, the ability of neutrophils to kill bacteria is enhanced when bacteria are first opsonized by antibodies produced by T and B cells. Antigen-presenting cells (APC) of the innate immune system, such as dendritic cells, support the activation of T and B cells of the adaptive immune system.

Pathophysiology, Risk Factors and Incidence

There are several types of plasma cell disorders that involve abnormal plasma cells but do not meet the criteria to be called active multiple myeloma. Following is a list of these plasma cell disorders. Only monoclonal gammopathy of undetermined significance and smoldering multiple myeloma in addition to active multiple myeloma will be covered in this learning program.

Table 1. Overview of Characteristics of Cells of the Immune System

Cell type	Origin	Function
B cells	Mature in the bone marrow; involved in the humoral immune response, essential component of the adaptive immune system	B cells produce antibody molecules which may be secreted or inserted into plasma membrane where they act as a part of B-cell receptors. When activated by an antigen, the B cell differentiates into a plasma cell. B cells present antigens and secrete cytokines.
T cells	Mature in the thymus; Involved in cell-mediated immunity, component of the adaptive immune system	Subdivided into helper and cytotoxic T cells; helper cells release cytokines to stimulate a defence against a specific antigen; cytotoxic T cells have TCR receptors on surfaces that kill viral cells when the receptor encounters a viral antigen
Natural Killer (NK) cells (also referred to as large granular lymphocytes	Differentiate and mature in the bone marrow, lymph nodes, spleen, tonsils and thymus; critical to the innate immune system, also play a role in the adaptive immune response. Research being conducted on NK role as a potential cancer therapy.	Provide rapid response to virally infected cells and respond to tumor formation causing cell death by apoptosis. Can recognize and kill stressed cells in the absence of antibodies and MHC; do not require activation to kill cells that are missing "self" markers of MHC class I.
Natural Killer T (NKT) cells	Share properties of both T cells and NK cells;	NKT cell activity promotes NK cell activity through secretion of interferon gamma, IL-4 and granulocytes-macrophage colony -stimulating factor and other cytokines and chemokines; dysfunction or deficiency of NKT cells may lead to development of autoimmune diseases such as diabetes, autoinflammatory diseases
Antigen Presenting Cells (APC), Dendritic Cells	Derived from myeloid precursor cells in the bone marrow; Component of the adaptive and innate immune systems	Capture and present antigens to activate T and B cell receptors arising from monocytes. Produce high levels of type I interferon and play a role in host antiviral defences and autoimmunity
Macrophages	Component of the adaptive and innate immune systems	Provide rapid and comprehensive response to pathogens; important for the body's defences

MHC, major histocompatibility complexes; TCR, T cell receptor
Based on Noonan 2015; Warrington 2011

- Monoclonal gammopathy
- Monoclonal gammopathy of undetermined significance (MGUS)
- Solitary plasmacytomas
- Smoldering multiple myeloma (SMM)
- Light chain amyloidosis
- Waldenstrom macroglobulinemia

Pathophysiology

Multiple myeloma is a malignant disease of plasma cells that results in overproduction of light and heavy chain monoclonal immunoglobulins. The disease is often characterised by bone marrow plasmacytosis, monoclonal protein production, osteolytic bone lesions, renal disease, anemia, hypercalcemia, and/or immunodeficiency.

Although the pathophysiology of multiple myeloma is very complicated, it is also well organised and consists of sequential interactions. Symptomatic myeloma is typically preceded by an asymptomatic, premalignant phase which, when recognised, is referred to as either monoclonal gammopathy of undetermined significance (MGUS) or smouldering multiple myeloma (SMM), depending on the extent of bone marrow involvement and the monoclonal protein (**Table 2**) (Morgan 2012; Rajkumar 2013). Smouldering multiple myeloma (SMM) is an intermediate stage between MGUS and active myeloma. All patients with active myeloma once had MGUS however only 20 % of patients with MGUS actually progress to active myeloma. The risk of progression from MGUS to myeloma is 1 % per year, and the risk of progression from SMM to myeloma is approximately 10 % per year (**Figure 3**). The transition to myeloma is then defined by the appearance of monoclonal plasma cells.

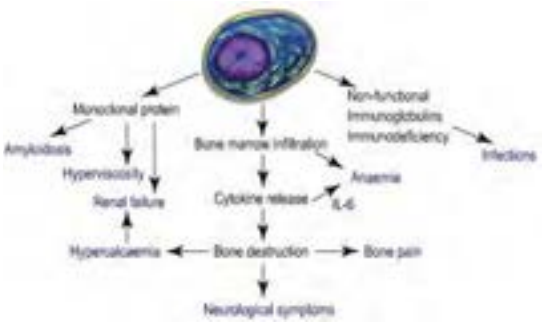

Figure 3. The effect on the body of plasma cell displacement of bone marrow: biological features of myeloma.

Underlying molecular variations affect the clinical course of myeloma. While some patients experience long periods of indolent disease, others relapse early and are refractory to therapy throughout the trajectory of their disease (Noonan 2021). Improvements in outcome are closely related to an evolving understanding of chromosomal abnormalities that influence staging, survival and treatment choice.

Normally, plasma cells make up about 4 % of the composition of the bone marrow: in myeloma, the plasma cell concentration can be greater than 10 %. The basic premise underlying progression to myeloma is that

Table 2. Definitions of MGUS, SMM and Multiple Myeloma

Monoclonal gammaopathy of undetermined significance (MGUS)	Monoclonal protein present but usually < 3.0 g/dL No CRAB features or other indicators of active myeloma Bone marrow monoclonal plasma cells < 10 %
Smoldering multiple myeloma (SMM)	Higher level of disease than MGUS; serum monoclonal protein ≥ 3.0 g/dL or Bence-Jones protein ≥ 500 mg/24h and/or bone marrow plasma cells > 10 % and < 60 % and absence of myeloma defining events (MDE) or amyloidosis
Myeloma based on CRAB	Presence of monoclonal protein and One or more CRAB features and/or indicators of organ damage

CRAB:
C = Calcium elevation (> 11 mg/dL)
R = Renal dysfunction (serum creatinine > 2 g/dL decrease from patient's normal value
A = Anemia (hemoglobin < 10 g/dL or > 2 g/dL decrease from patient's normal value
B-Bone disease ≥ 1 osteolytic lesion detected on skeletal radiography, CT or PET/CT
[Procedures and tests used to diagnose and stage myeloma are detailed in Module 2]
Sources: NCCN 2024; Noonan 2021

multiple mutations in different pathways deregulate plasma cell biology, producing changes that lead to the development of clinical features of myeloma (Morgan 2012).

As the disease progresses, myeloma plasma cells are no longer confined to the bone marrow. They can be found in extramedullary locations and as circulating leukaemia cells. It appears that the transition of these different phases is due to the acquisition of genetic abnormalities that lead to the development of the biological characteristics of myeloma (**Figure 3**).

The role of genetics in multiple myeloma

Active multiple myeloma develops over a period of time from several complex genetic events. The process begins early with premalignant stages of the myeloma (i.e., MGUS and smoldering myeloma)and are extremely common (Fonesca 2004; Robiou de Pont 2017). Specific chromosomal abnormalities have been identified involving translocations, deletions or amplifications and are identified using metaphase cytogenetics, conventional karyotyping or fluorescence in situ hybridization (FISH) analysis [see Module 2].

Chromosomal abnormalities of importance for prognostic and treatment recommendations include:

-Translocation involving immunoglobulin (Ig) heavy chain locus or nonhyperdiploidy: Translocation of t(4;14), t(14;16), t(14;20) associated with poor prognosis, present in approximately 10 %-20 % of newly diagnosed patients

-Hyperdiploidy or trisomies involving odd chromosomes (3, 5, 7, 9, 11, 15, 19, 21) generally associated with a more favorable outcome:

-Abnormalities of chromosome 1: gains/amplification of 1q21 (long arm) increases risk of myeloma progression and incidence of the amplification is higher in relapsed than in newly diagnosed patients

-Deletion of 17p13 (the locus for the tumor-suppressor gene, p53): causes loss of heterozygosity of TP53 and is considered a high-risk feature of myeloma (NCCN 2024).

Research suggests that defining high-risk characteristics, such as those found in the bone marrow microenvironment, will provide key information for prognostic counseling, and selection and sequencing of treatment.

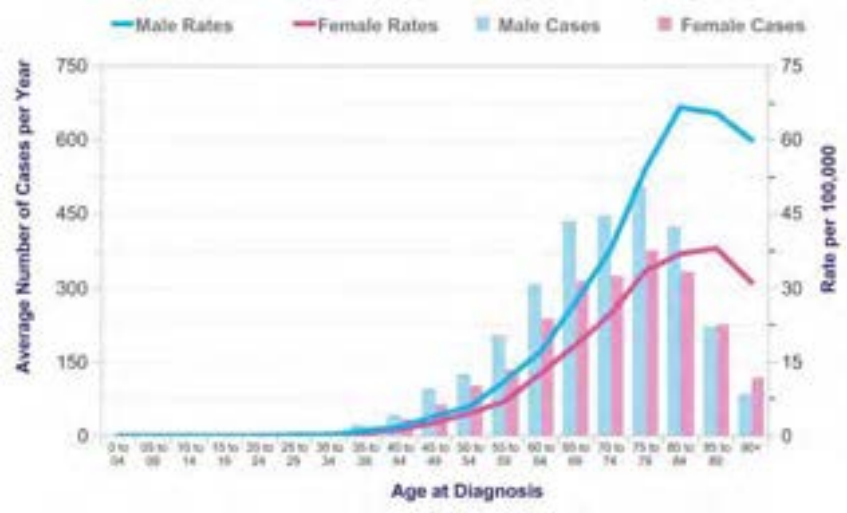

Figure 4. Mean number of new cases of multiple myeloma per year and by age, UK, 2016-2018.
Source: Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-One

Risk Factors

The cause of multiple myeloma is poorly understood, in part due to the low incidence of the disease. MGUS is one of the most important risk factors. Other risk factors include increasing age, male sex, family history, Black race and genetic factors. The factors contributing to progression from MGUS to myeloma are unclear.

Several lifestyle and environmental factors have been evaluated as risk factors for myeloma. Agricultural or industrial occupations are acknowledged as risks (i.e., those that involve exposure to benzene, petroleum products or Agent Orange). Evaluation of obesity and dietary characteristics has yielded conflicting epidemiological data although there is evidence of a relationship between these factors are and an increased risk of myeloma (Marinac 2019; Sergentanis 2015).

Incidence

Compared to other cancers, myeloma is relatively rare. Multiple myeloma accounts for approximately 1 % of all newly diagnosed cancers worldwide. This corresponds to 176,404 new cases in 2020. Global mortality was 117,077 in the same year (Globocan 2020). Because the median age at diagnosis is about 70 years, the rapidly aging world population means the incidence of myeloma is likely to rise significantly to about 350,000 cases by the year 2050 (Ludwig 2013).

The incidence of multiple myeloma is unevenly distributed around the world. The highest occurrence is in the industrialised regions of Australia/New Zealand, Europe and North America. According to data from the UK, the rate of multiple myeloma increases sharply between the ages of 55 and 59, with a peak in men and women aged 85 to 89 and women aged 85 to 89 (**Figure 4**) (Cancer Research UK 2021). The American Cancer Society has estimated 35,730 new myeloma cases and an estimated 12,590 deaths in the US in 2023 (Siegel 2023).

There is an increasing trend of multiple myeloma incidence globally, particularly in men, people aged 50 years or older, and those from high-income countries. On a positive note, there is an overall decreasing trend of multiple myeloma mortality over time and this trend is more evident in women (**Figure 5**) (Huang 2022).

Relative survival is an estimate of the percentage of patients who would be expected to survive the effects of their cancer. Because no two patients are exactly alike and treatment and responses to treatment can vary greatly, survival statistics cannot be used to predict exactly what will happen to an individual patient. The 5-year relative survival for patients with myeloma according to the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) has dramatically improved over the past 4 decades, primarily due to the availability of new treatments (SEER 2023). The 5-year relative survival rate for myeloma in the US (all races and ethnicities, men and women) was 25 % for the period 1975-1977, increasing to 58 % for the period 2012-2018 (Siegel 2023). A decreasing mortality rate from multiple myeloma is partly due to the large number of new myeloma therapeutics that have significantly expanded treatment options. However, global treatment outcome and survival show significant disparities in terms of under-awareness and sub-optimal treatment in some regions of the world, particularly low-income countries. This shows the importance of economic resources and access to and quality of the healthcare system for better diagnosis and survival of myeloma patients (Ludwig 2020).

Despite very good therapeutic measures, myeloma cannot yet be cured at the present time. However, advances in understanding the causes of multiple myeloma, including knowledge of the genetic abnormalities underlying myeloma and the availability of more effective therapeutic options for patients, have resulted in improved overall patient survival. Patients are now dying with their disease instead of from their disease. New therapeutic options with different mechanisms of action have also contributed to improving the quality of life of patients with myeloma [see Module 3].

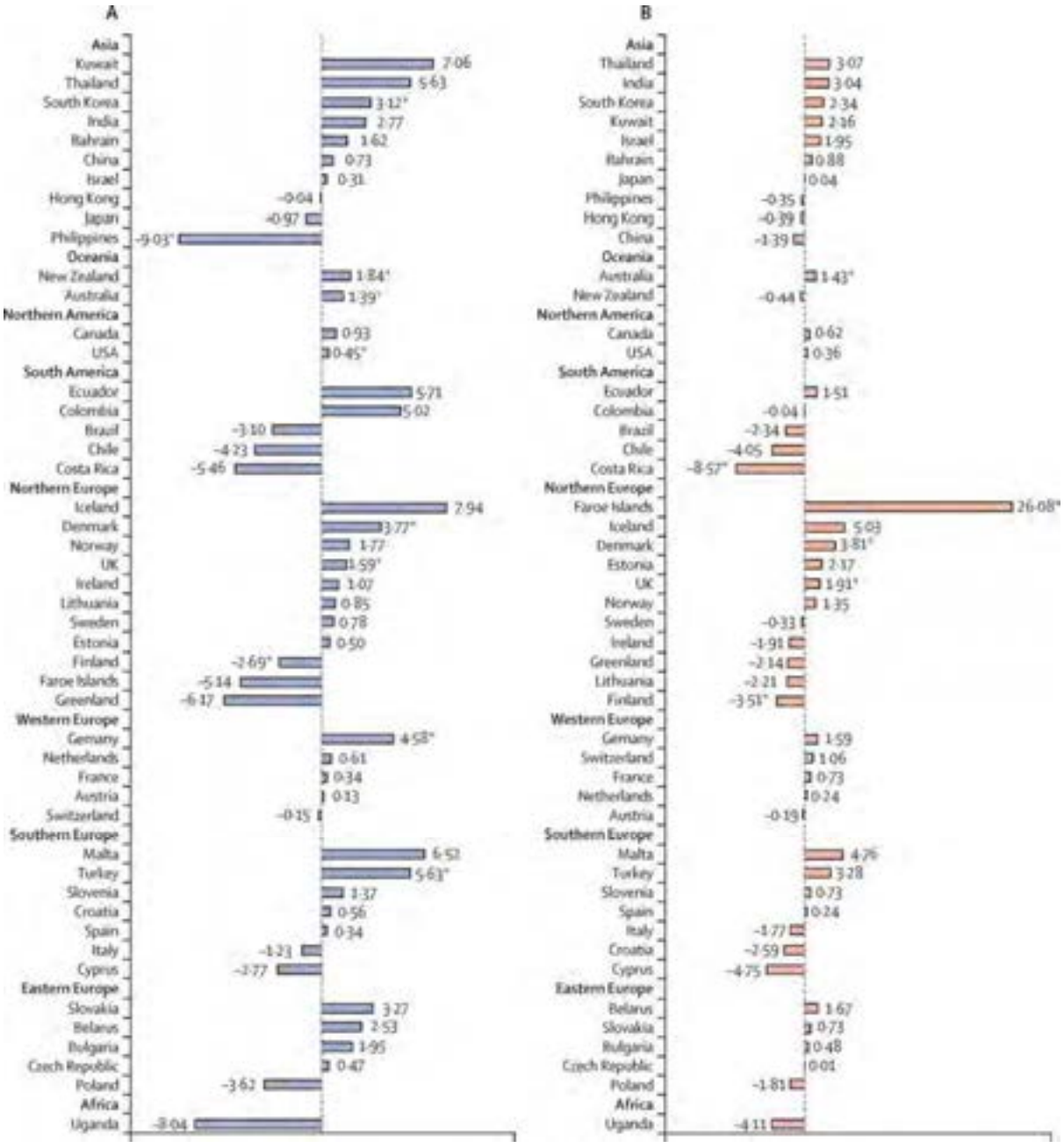

Figure 5. Average annual percentage change of multiple myeloma incidence in all men (A) and women (B) from 2001 to 2019 (Huang 2022).

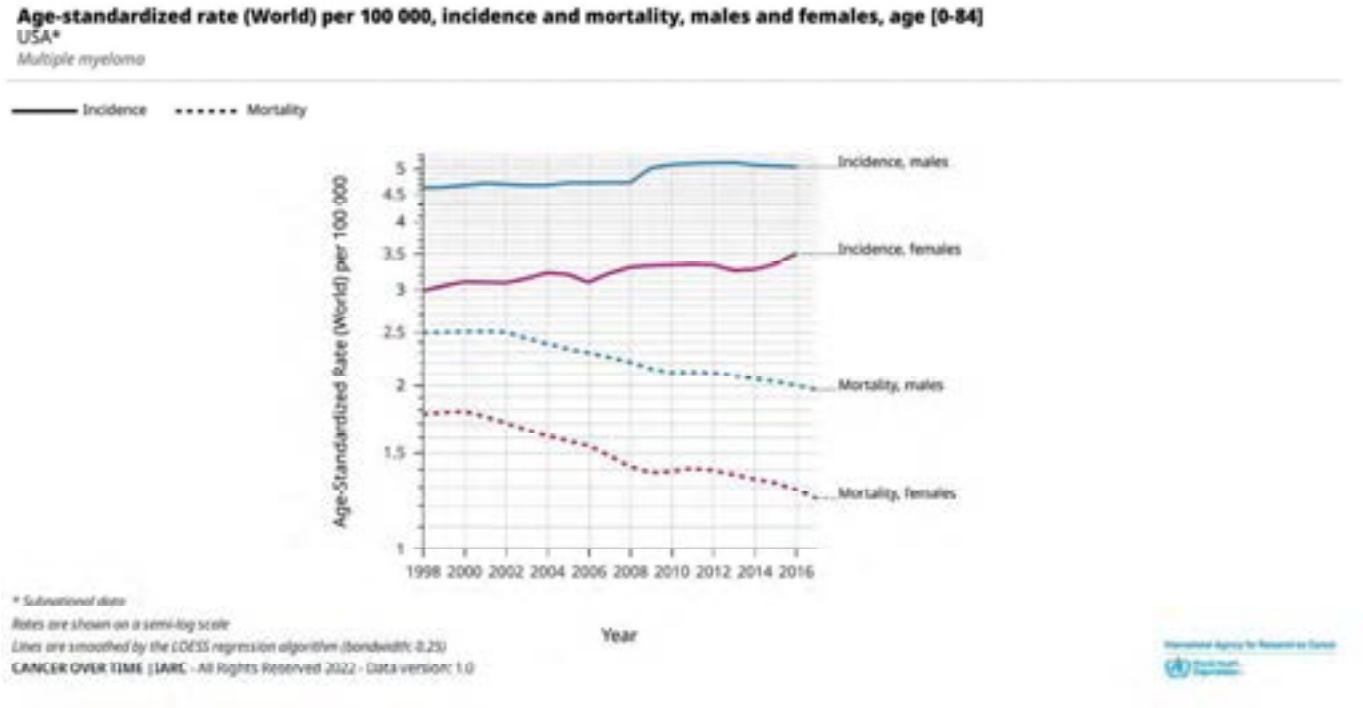

Figure 6. Age-standardised rate of incidence and mortality per 100,000, broken down by sex, in the United States

Future Perspectives

The International Myeloma Foundation (IMF) launched the Black Swan Initiative in 2012 with the goal of finding a cure for multiple myeloma. Important steps towards this goal are possibilities for prevention, early initiation of interventions in SMM stage and diagnostic possibilities for testing for minimal residual disease (MRD) (IMF 2022).

Resources	
American Cancer Society (ACS) www.cancer.org	American Cancer Society, online resources on cancer
American Society for Blood and Marrow Transplantation (ASBMT) www.asbmt.org	American Society for Bone Marrow Transplantation, Educational Services, Clinical Standards and Research
European Myeloma Network (EMN) http://myeloma-europe.org	Research network for the development of diagnostics and therapy for multiple myeloma
European Oncology Nursing Society (EONS) www.cancernurse.eu	European Organisation of Nurses in Oncology
European Society for Blood and Marrow Transplantation (EBMT) www.ebmt.org	European professional association promoting all aspects of cellular therapies
European Society for Blood and Marrow Transplantation – Nursing Section https://www.ebmt.org/nurses-group	Organisation of nurses within the EBMT
International Myeloma Foundation (IMF) www.myeloma.org	Myeloma information, treatment, research, support in multiple languages
Nurse Leadership Board of the International Myeloma Foundation https://www.myeloma.org/nurse-leadership-board	Education and standards of care for multiple myeloma
Multiple Myeloma Research Foundation (MMRF) www.themmrf.org	Myeloma information, research efforts and support
Myeloma UK www.myeloma.org.uk	Professional and patient information; Vocational training
National Cancer Institute www.cancer.gov	Information on disease types and research

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Quick Facts

- The International Myeloma Working Group (IMWG) definition of multiple myeloma now includes biomarkers (identified by the acronym SLiM) in addition to requirements of CRAB (increased **C**alcium level, **R**enal dysfunction, **A**nemia, destructive **B**one lesions
- Many clinical features of multiple myeloma are related to proliferation of plasma cells in the bone marrow
- Nearly all patients present with fatigue at diagnosis; 15 % have infections, 50 % renal insufficiency and 17 % hypercalcemia
- Cytogenetic abnormalities are becoming increasingly important in classifying the different categories within multiple myeloma and estimating prognosis
- The Revised International Staging System (R-ISS) takes into consideration clinical presentation and cytogenetic abnormalities to stage multiple myeloma

Module II: Multiple Myeloma: Diagnosis and Staging

Introduction

Multiple myeloma is a cancer of plasma cells. Normal plasma cells are found in the bone marrow and play an important role in the immune system [see Module 1]. The development of myeloma is a complex multistep process. It is difficult to diagnose multiple myeloma in its early stages as it often causes no symptoms until an advanced stage is reached.

Plasma cells, a type of B cells, produce antibodies (or immunoglobulins) that attack and kill pathogens [see Module 1]. In multiple myeloma, the growth of plasma cells, found mainly in the bone marrow, becomes unregulated and they produce an abnormal protein or antibody known by several different names including monoclonal immunoglobulin and monoclonal protein (M-protein). The change from normal, regulated plasma cell growth initiates a cascade of medical issues and conditions that affect the function of bone marrow and kidneys and lead to pathologic changes in bones.

Typically, myeloma is preceded by monoclonal gammopathy of undetermined significance (MGUS), an asymptomatic condition. MGUS can lead to smoldering multiple myeloma (SMM) or asymptomatic multiple myeloma. Both conditions can progress to symptomatic multiple myeloma. Research suggests that patients with a high risk of progression to symptomatic disease may benefit from early therapy [see Module 3] with an increase in survival time if treatment is initiated before serious organ damage occurs.

Diagnosis

The diagnosis of monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and active multiple myeloma is based on clinical, biologic and radiologic presentation. In almost all patients, multiple myeloma begins as MGUS, which is a clonal plasma cell dyscrasia present in 3 % to 5 % of people older than 65 years and in 10 % of those older than 80 years (Crawford 1987). SMM is a more advanced plasma cell disorder. Approximately 10 % of patients with SMM progress to multiple myeloma. Both MGUS and SMM are commonly discovered incidentally after further evaluation of abnormal laboratory values. Some of the abnormal values include an increase in total protein or globulin and an abnormal serum protein electrophoresis panel (SPEP) obtained for a variety of symptoms such as neuropathy, an increase in infections and chronic inflammatory demyelinating polyneuropathy (Noonan 2021).

Monoclonal gammopathy of undetermined significance (MGUS)

A diagnosis of MGUS is one made after excluding the presence of SMM and active multiple myeloma. The hallmark clinical feature of MGUS is an increase in plasma cells not associated with clinical symptoms or high-risk laboratory abnormalities such as hypercalcemia, renal impairment, anemia and osteolytic bone lesions (**Table 1**). Bone marrow biopsy and aspiration should be considered in patients suspected of having MGUS along with cytogenetic testing with fluorescence in situ hybridization (FISH). Patients with a confirmed diagnosis of MGUS should be monitored closely for disease transformation to SMM or active multiple myeloma. Follow-up should be scheduled every six months if clinical status remains stable (Noonan 2021).

A new classification of MGUS, monoclonal gammopathy of clinical significance (MGCS), was developed for patients with MGUS who have organ dysfunction. MGCS is subdivided into monoclonal gammopathy of renal significance and monoclonal gammopathy of neurological significance, depending on the nature of organ or system involvement (NCCN 2024).

Table 1. Diagnostic Criteria for MGUS, SMM and Active Multiple Myeloma (Adapted from International Myeloma Working Group Updated Criteria[a])

Non-IgM MGUS	SMM	Active Multiple Myeloma
All three criteria must be met: 1. Serum M-protein (non-IgM) < 30 g/L 2. Clonal bone marrow plasma cells < 10 % 3. Absence of end organ damage that can be attributed to the plasma cell proliferative disorder (e.g., CRAB features, amyloidosis)	Both criteria must be met: 1. Serum M-protein (IgG or IgA) ≥ 30 g/L or urinary M-protein > 500 mg/24h and/or clonal bone marrow plasma cells 10 %-60 % 2. Absence of myeloma-defining events or amyloidosis	Both criteria must be met: 1. Clonal bone marrow plasma cells ≥ 10 % or biopsy proven plasmacytoma 2. One or more myeloma-defining events (see Table 2)

MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma
Sources: [a]Rajkumar 2014; Sive 2021; Cowan 2022

Smoldering multiple myeloma (SMM)

SMM is an asymptomatic clonal plasma cell disorder. The risk of progression to multiple myeloma is 10 % per year during the first 5 years following diagnosis, decreasing to 3 % per year over the subsequent 5 years, and 1 % per year after the 10 years of diagnosis (Kyle 2007).

Recommended baseline evaluation procedures for SMM:
• CBC • Serum electrolytes, BUN, creatinine • Serum and urine electrophoresis and immunofixation • Bone marrow evaluation • F-FDG PET-CT scan or MRI
BUN, blood urea nitrogen; CBC, complete blood count; F-FDG, F-fluorodeoxyglucose; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computerized tomography Source: Visram 2021

The International Myeloma Working Group (IMWG) identifies two criteria that must be met to establish a diagnosis of SMM (**Table 1**). Most clinical trials base study eligibility on these established criteria.

In 2020, the IMWG undertook a study to identify factors that predicted progression to active multiple myeloma with the goal of developing a risk score to predict the 2-year progression risk (Mateos 2020). Factors predicting progression were M-protein (> 2 g/dL), bone marrow plasma cells infiltration (> 20 %) and a > 20 ratio of involved versus uninvolved serum free light chain. Patients with these factors had a 50 % progression risk to myeloma at 2 years from diagnosis.

Active multiple myeloma

The goal of diagnostic testing in patients suspected of having myeloma is to establish an accurate diagnosis and determine the extent of the disease, which subsequently aids in establishing a prognosis. Myeloma should be diagnosed using the 2014 IMWG updated criteria (Rajkumar 2014) (**Table 1**).

Clinical presentation

The clinical presentation can vary from completely asymptomatic to life-threatening symptoms, depending on the stage at which the disease is diagnosed. Myeloma should always be considered in older patients with back pain (back or ribs) and constitutional symptoms such as sweating and weight loss.

Because multiple myeloma originates in the bone marrow, many signs and symptoms at presentation can be attributed to pathological changes taking place in the marrow. Fatigue related to anemia occurs in nearly all patients with active disease and an increase in infections, particularly bacterial infections, in approximately 15 % (Noonan 2021). Renal insufficiency (due to the accumulation of monoclonal light chains in the kidneys that obstruct tubules and glomeruli) is present in approximately 50 % of patients at diagnosis (Vakiti 2022), and hypercalcemia (caused by osteolytic bone lesions) is reported in approximately 17 % of newly diagnosed patients (Bao 2020).

Typical signs and symptoms of multiple myeloma include:

- Bone problems: pain, weakness, fractures (especially in the spine, chest or hips)
- Low blood counts causing anemia, fatigue, bleeding risk (especially mucosal bleeding)
- High blood levels of calcium causing thirst, frequent urination, dehydration, kidney problems/failure, constipation, abdominal pain, loss of appetite, general weakness, confusion
- Nervous system: peripheral neuropathy; pain, leg numbness, leg weakness in the presence of spinal cord compression
- Renal insufficiency
- Headaches
- Visual disturbances (Cowan 2022; Pawlyn 2019; Ramsenthaler 2016).

History and physical examination

The initial diagnostic workup should include a history and physical examination. History should include information about comorbidities such as coronary artery disease, heart failure, hypertension, kidney and liver disorders, and lung disease, all disorders that could affect treatment decision-making.

Laboratory evaluation

Typical of myeloma is the monoclonal protein (M protein), which is produced by the degenerated plasma cells and can be detected in blood and/or urine. In approximately 86 % of people with multiple myeloma, the serum-protein electrophoresis reveals a monoclonal protein, defined as the presence of an atypical antibody in the blood. A 24-hour urine protein test to quantify Bence-Jones protein is important to document the presence of baseline proteinuria and evaluate for evidence of secondary light-chain amyloidosis (**Table 3**) (Cowan 2022).

Radiographic and imaging studies

The standard examination for multiple myeloma is whole-body computed tomography (CT), or ideally functional imaging such as computed tomography-positron emission tomography (CT-PET) or diffusion weighted whole body

magnetic resonance imaging (MRI) (Sive 2021; Cowan 2022) to assess the extent of skeletal involvement, especially in the spine, shoulders, chest, pelvis and arm and leg bones (**Table 3**). Pathological fractures of long bones, ribs or vertebral bodies are common in newly diagnosed patients taking corticosteroids and are often the reason the patient seeks medical attention (Howell 2018).

Bone marrow evaluation

The proliferation of monoclonal plasma cells is determined by bone marrow sampling and/or bone marrow biopsy (Dimopoulos 2021). Performance of a bone marrow aspirate and biopsy is essential for establishing a diagnosis of multiple myeloma (Sive 2021).

Tests conducted on bone marrow samples should include morphology of plasma cells; quantification of CD138+ plasma cells in the core biopsy by immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH) and conventional cytogenetics (**Table 3**) (Cowan 2022).

Myeloma-defining events

End organ damage is no longer required to diagnose myeloma. The IMWG definition of multiple myeloma now includes biomarkers (identified by the acronym SLiM) in addition to requirements of CRAB features (**Table 2**). Each of the three biomarkers is associated with an approximately 80 % probability of the development of CRAB features (hypercalcemia, renal impairment, anemia and bone disease) (Sive 2021). The presence of osteolytic bone lesions >5mm on CT or PET-CT is consistent with a myeloma-defining event; increased uptake on PET-CT alone, without corresponding lytic lesions, is insufficient to be a myeloma-defining event but is associated with an increased risk of progression to myeloma (Rajkumar 2014).

Table 2. Myeloma-defining Events (International Myeloma Working Group Updated Criteria[a]

Myeloma-defining event
[**S**] ≥ 60 % plasma cells in marrow
[**Li**] Involved: uninvolved light chain ratio ≥ 100 (provided the involved light chain is > 100 mg/L)
[**M**] 2 or more focal lesions on MRI (> 5 mm in size)
[**C**] Increased **C**alcium: (> 2.75 mmol/L or > 0.25 mmol/L higher than upper limit of normal)
[**R**] **R**enal insufficiency: (serum creatinine > 177 µmol/L or creatinine clearance < 40 ml/min[b])
[**A**] **A**nemia: Hb < 100 g/L or 20 g/L below lower limit of normal
[**B**] 1 or more lytic **B**one lesion on X-ray, CT or PET-CT[c] (> 5 mm in size)

CT, computerized tomography; Hb, hemoglobin; MRI, magnetic resonance imaging, PET, PET-CT, positron emission tomography computerized tomography; SLiM, Sixty, Light chain ration MRI
Sources: [a]Rajkumar 2014; Sive 2021; [b]Creatinine clearance measured or estimated; [c]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

Table 3. Multiple Myeloma Diagnostic Procedures

Diagnostic Procedures	Description and Clinical Significance
	Blood chemistry
Beta-2 microglobulin	Correlates to systemic myeloma burden and is used in staging
Blood urea nitrogen, creatinine	Kidneys are affected by aggressive myeloma, which is measured by an increase in creatinine and blood urea nitrogen
Calcium	Increases in calcium and alkaline phosphatase caused by bone disease
Electrolytes	Imbalances could reflect renal dysfunction. Decrease in sodium often seen in patients with high protein levels
Liver function tests, alkaline phosphatase, albumin	Increases in calcium and alkaline phosphatase caused by bone disease. Albumin levels decreased
Total protein, globulin	Immunoglobulins are proteins; total protein often elevated, and most is globulin

Table 3. Multiple Myeloma Diagnostic Procedures

Diagnostic Procedures	Description and Clinical Significance
Complete blood count with differential	
Platelets	Decreased with significant bone marrow involvement
Red blood cells	Decreased, anemia common at diagnosis
White blood cells	May be elevated in plasma cell leukemia
Diagnostic imaging	
Low-dose whole-body CT, MRI, PET, PET-CT, PET-MRI	Detects bone involvement and plasma-cytoma found in bone or soft tissue; can be used to track disease progression and treatment response; PET-CT useful in detecting extramedullary disease outside of the spine.
Bone marrow biopsy and aspirate	
Cellular assessment and bone marrow plasma cell quantification	Cellular assessment measures disease burden and is used in staging;
Chromosomal abnormalities (chromosome analysis and FISH) to detect unfavorable cytogenetic aberrations	Cytogenetic findings are used to evaluate and categorize risks (see **Table 4**)
Monoclonal proteins	
Immunoglobulins: IgG, IgA, IgM	Plasma cells produce antibodies (immunoglobulins). An increase in plasma cells produces IgG or IgA; an increase in IgM is less common
Monoclonal proteins	Malignant plasma cells secrete a monoclonal protein (M protein)
Serum protein electrophoresis (SPEP) Urine protein electrophoresis (UPEP) (24-hour urine collection)	Separates proteins in blood or urine into several groups based on size and electrical charge; quantification of M protein, defined as the presence of an atypical antibody in the blood. Provides information on total protein; quantifies Bence-Jones protein to document the presence of baseline proteinuria and evaluate for evidence of secondary light-chain amyloidosis, which often manifests as nephrotic range proteinuria.
Serum immunofixation electrophoresis	Identifies specific information about the type of M protein present; assessment of changes in levels of various proteins, particularly the M protein, can be used to track disease progression and treatment response
Serum-free light chain assay (serum)	Screens for myeloma and related plasma cell disorders by indicating presence of M protein; helpful in prognostication of MGUS, SMM, active myeloma, immunoglobulin light chain amyloidosis and solitary plasmacytoma; used to document stringent complete response according to IMWG response criteria; greater sensitivity than SPEP or UPEP
Additional laboratory parameters	
Albumin, β2-microglobulin, LDH, CRP, CBC and differential, peripheral blood smear, chemistry screen	Provide information for disease staging (albumin and β2-microglobulin), organ function and disease aggressiveness (LDH), bacterial infections (CRP)
Nephelometry of serum immunoglobulin	Measurement of IgA, overestimates M protein concentration in patients with IgG and IgM myeloma. Provides information about suppression of non-involved immunoglobulins.

CBC, complete blood count; CT, computed tomography; CRP, C-reactive protein; FISH, fluorescence *in situ* hybridisation; IMWG, International Myeloma Working Group; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography
Adapted from: Ludwig 2014; Dimopoulos 2021; Sive 2021; NCCN 2024; Noonan 2021

Staging Systems

The International Staging System (ISS) is a simple risk stratification algorithm based on the important biological parameters, serum beta2-microglobulin (β2M) and serum albumin (**Table 4**) (Palumbo 2015). Biomarkers and genetic abnormalities influence treatment response and the ISS does not account for these factors. Following an evaluation based on 4,445 patients, Palumbo et al (2015) developed the R-ISS. The R-ISS takes into consideration clinical presentation and cytogenetic abnormalities across healthcare settings based on objective clinical similarities (Noonan 2021).

A limitation of the R-ISS is that most of the patients are classified as R-ISS II or the intermediate-risk group, which includes patients with large variations in risk of progression or death. The R2-ISS identifies four risk groups by assigning a numerical value to each risk factor based on their influence on overall survival: the low-risk group is 0 points, low-intermediate-risk group is 0.5-1 points, intermediate high-risk group is 1.5-2.5 points and high-risk group is 3-5 points. The R2-ISS is limited in that it has only been validated in newly diagnosed patients with multiple myeloma (D'Agostino 2022; NCCN 2024).

Table 4. International Staging System for Multiple Myeloma

Stage	Criteria (ISS)[a]	Criteria (R-ISS)[b]	Criteria (R2-ISS)[c]
I	Serum β_2 microglobulin < 3.5 mg/L AND serum albumin ≥ 35 g/L	ISS stage I and standard-risk chromosomal abnormalities by FISH and Serum LDH ≤ upper limit of normal	Low-risk Not ISS stage II or III Serum LDH ≤ upper limit of normal del(17p) or t(4;14) or 1Q+ not detected
II	Not fitting criteria for stage I or III	Not R-ISS stage I or III	Low-intermediate risk ISS stage II or Serum LDH. high/upper limit of normal or Del(17p) or t(4;14) or 1q+ detected
III	Serum β_2 microglobulin ≥ 5.5 mg/L (irrespective of albumin value)	ISS stage III and/or high-risk chromosomal abnormalities by FISH or serum LDH > upper limit of normal	Intermediate-high risk Any combination of high-risk features equaling a score of 1.5-2.5
IV			High-risk Any combination of high-risk features equaling a score of 3-5

ISS, International Staging System; R-ISS, Revised-ISS; R2-ISS, Second revision of ISS
Sources: [a]Greipp 2005; [b]Palumbo 2015; [c]D'Agostino 2022

Prognostic factors

Patient survival depends on the stage of the disease. Patients with suspected myeloma should be referred to a specialized oncologist or hematologist for diagnostic work-up and staging.

Cytogenetic analysis should be undertaken by interphase FISH (fluorescence in situ hybridization) on CD138-selected bone marrow cells. A number of cytogenetic abnormalities are of prognostic significance in newly diagnosed patients (Table 5). Data from randomized controlled trials using modern therapy show that the median survival in multiple myeloma is approximately 6 years (42), with a median survival of 8 years in patients who undergo allogeneic stem cell transplant (44, 45). Median survival is lower in older patients.

As in other cancers, overall survival in multiple myeloma is affected by patient characteristics, tumor burden (stage), biology (cytogenetic abnormalities) and response to therapy. In addition to cytogenetic risk factors, two other markers associated with aggressive disease biology are elevated LDH and evidence of circulating plasma cells on routine peripheral smear examination (also referred to as plasma cell leukemia). The R-ISS takes these factors into consideration to estimate prognosis which supports clinical care and helps in comparison of clinical trial results. However, because treatment options have significantly improved over the past decade, there is a need to stratify multiple myeloma based on individual cytogenetic groups

Table 5. Prognostic Significance of Cytogenetic Abnormalities in Newly Diagnosed Myeloma

Standard risk	Intermediate/High risk
Trisomies t(11;14) (q13;q32) t(6;14) (p21;q32) Trisomies plus any one of the IgH translocations may ameliorate adverse prognosis conferred by high risk IgH translocations and del 17p Hyperdiploidy	t(4;14) (p16;q32): – Intermediate risk t(14;16) (q32;q23): High-risk t(14;20) (q32;q11): High-risk Del(17p): High-risk **Gain(1q21): Intermediate risk** **High-risk gene expression profile** **Risk factors for disease progression and/or relapse (newly diagnosed patients):** **Diagnosis as Revised International Staging System (R-ISS) III** **Presence of extramedullary disease** **Presence of circulating plasma cells**

Sources: Rajkumar 2022; NCCN 2024; Sive 2021

rather than arbitrary heterogeneous risk categories (Rajkumar 2022). Nevertheless, a greater understanding of pathophysiology and the role of genetic abnormalities in myeloma have provided the basis for clinical advancement with an improvement in the overall survival of patients with myeloma.

Clinical Manifestations of Multiple Myeloma in Symptomatic Patients at Initial Presentation requiring Immediate Management

Multiple myeloma is a malignancy that affects the bone marrow. Many of its clinical manifestations are therefore derived from the diffuse infiltration of the bone marrow and the destruction of bones (Talamo et al., 2010). Evidence of tissue or organ disorders is an essential criterion for deciding whether treatment should be started. According to a population-based study in the UK, the most frequent route to diagnosis, accounting for roughly one-third of cases, is emergency presentation to the hospital (Howell 2017), suggesting that patients were unaware of the severity of their condition. As might be expected, the impact on survival for patients presenting at the emergency department was immediate; the overall survival and relative survival estimates of these patients was markedly poorer from that of patients with a first presentation at non-emergency facilities within 3 months of diagnosis.

Hypercalcemia

About 17 % of patients present with hypercalcaemia (Bao 2020), which usually occurs as part of a symptomatic illness. Signs and symptoms of hypercalcaemia may include:

- Nervous system disorders (confusion, coma and impaired consciousness)
- Muscle weakness
- Inflammation of the pancreas
- Constipation
- Thirst
- Polyuria
- Shortening of the Q-T interval on electrocardiogram
- Acute renal failure

Mild hypercalcaemia (calcium 2.6-2.9 mmol/L) can be managed by oral and/or intravenous rehydration. Moderate or severe hypercalcaemia (calcium ≥ 2.9 mmol/L) should be treated with intravenous administration of normal saline. Adequate urinary outflow should be ensured by administration of a loop diuretic to prevent volume overload and to promote renal excretion of calcium (**Table 6**).

[Management of hypercalcaemia is covered in more detail in Module 4.]

Renal insufficiency

Kidney dysfunction is a common and potentially dangerous complication of myeloma. About 20 % of patients have renal insufficiency (defined as elevated serum creatinine > 2 mg/dL or established glomerular filtration rate < 60 mL/min/1.73 m^2) at the time of diagnosis (Dimopoulos 2021). This is reversible in most patients after initiation of treatment for myeloma. In some patients, however, permanent renal dysfunction can manifest itself, which can lead to renal replacement therapy. Kidney failure occurs due to damage caused by light chain cast nephropathy,

but other etiologies should be considered including hypcalcemia, volume depletion and hyperuricemia as well as nephrotoxic medications or IV contrast (NCCN 2024). Patients presenting with renal insufficiency have a higher risk of mortality (**Table 6**).

[Management of renal insufficiency is covered in more detail in Module 4.]

Bone pain

Bone disease resulting from lytic bone injury can be either focal or diffuse and can cause pain, pathologic fracture/spinal compression, and hymercalcaemia. Bone pain occurs in 60 % of patients at diagnosis and 60 % of patients sustain pathologic fractures during disease progression (Melton 2005). Bone lesions and their sequelae can limit activities of daily living and quality of life (Roodman 2009) (**Table 6**).

[Management of bone lesions and their sequela is addressed in Module 4.]

Suppression of hematopoietic function

As the bone marrow becomes filled with malignant plasma cells, the ability of hematopoietic stem cells to produce new blood cells is diminished leading to anemia, neutropenia and thrombocytopenia causing symptoms such as fatigue, infections and bleeding, respectively.

The presence of anemia at the time of diagnosis is often due to suppression of erythropoiesis by tumor-related cytokines, renal insufficiency, and/or vitamin and iron deficiencies (Katzel et al., 2007). The patient may have anemia-related symptoms such as shortness of breath, fatigue, or dizziness. Treatment of multiple myeloma often improves erythropoiesis and the administration of erythropoietin can correct symptomatic anemia (**Table 6**).

[Management of anemia is discussed in detail in Module 4.]

Table 6. Presenting Signs and Symptoms of Multiple Myeloma requiring immediate Management

Presenting sign/symptom	Management
Hypercalcemia	Hydration; monitoring of fluid status; administer bisphosphonates
Elevated creatinine/renal insufficiency	Provide adequate hydration either as IV infusion or orally, monitor fluid status to avoid hypervolemia; avoid nephrotoxic drugs; correct concomitant metabolic abnormalities (i.e., hypercalcemia, hyperuricemia); nephrology referral; administer allopurinol
Bone pain	Administer paracetamol or tramadol or other analgesic; avoid use of contrast material for CT until renal function stabilizes; palliative radiation therapy for impending cord compression and pain management
Pathologic fracture	Provide pain management; stabilize affected area; orthopedic referral
Infection	Perform cultures to identify pathogenic cause; administer antibiotics or antiviral agents; avoid nephrotoxic antibiotics
Anemia/low hemoglobin	Administer erythropoiesis-stimulating agents

CT, computerized tomography; IV, intravenous
Sources: Kumar 2020; Monteith 2023

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Quick Facts

- Regardless of whether a patient is eligible or ineligible for autologous stem cell transplantation (ASCT), the approach to treating myeloma should be based on individual factors such as features of the disease, patient age, presence of co-morbidities and personal preferences.
- Prior to the initiation of any treatment for multiple myeloma, issues related to supportive care should be taken into consideration to avoid early complications that may compromise therapeutic outcomes.
- Triplet or triple drug treatment [bortezomib/lenalidomide/dexamethasone (VRd) or daratumumab/lenalidomide/dexamethasone (DRd)] is the recommended standard first-line treatment in all transplant-eligible patients; this regimen provides improved response rates and depth of response, and longer progression-free survival/overall survival (PFS/OS) rates.
- Tandem ASCT (a second course of high-dose treatment and ASCT within 6 months of the first course) may be recommended for some patients, especially those with high-risk disease.
- A triplet regimen (VRd) or DRd) is also recommended for newly diagnosed non-transplant eligible patients; this regimen has shown superiority over a 2-drug regimen on PFS and OS rates.
- Median age at diagnosis is 69 and 33 % of patients are > 75 years at diagnosis. The goal of treating this population is to avoid undertreating the fit older patient while avoiding overtreating the frail older patient.
- Single agents are infrequently used to treat myeloma. Multiple drug regimens may exacerbate known side effects of individual drugs or cause drug-drug interactions. Knowledge of adverse events, their manifestations and preventative management is key to good oncologic practice.

Module III: Treatment of Multiple Myeloma

Introduction

Greater understanding of the microenvironment of the bone marrow has led to the use of new combinations of therapies and to the development of new drugs. While there is no cure for multiple myeloma, newly developed agents, and those currently in the pipeline, offer options to effectively manage the disease.

Because myeloma cells are dependent on the bone marrow microenvironment for growth and survival, disruption of the microenvironment may be effective in controlling the disease. Novel agents not only target the myeloma cell itself, but also mechanisms within the bone marrow microenvironment that underlie the genetic changes in cells leading to, in the case of multiple myeloma, the abnormal growth and division of plasma cells. Because different agents have different molecular targets, using agents with different mechanisms of action in combination may have a synergistic effect and provide a better treatment response.

The first step in evaluating treatment options for newly diagnosed patients with multiple myeloma is determining whether they are candidates for high-dose treatment and autologous stem cell transplantation (ASCT). Currently, advanced age and renal dysfunction are no longer absolute contraindications to transplantation, and all patients should be referred to a transplant center to assess eligibility for ASCT. According to international guidelines, induction treatment followed by high-dose treatment with ASCT is recommended for newly diagnosed patients with multiple myeloma who are in good health and do not have compromising comorbidities. In two studies comparing upfront ASCT versus systemic treatment after triplet novel agent-based induction treatment, progression free survival (PFS) was improved in the arm with early ASCT (Attal 2017; Cavo 2020). There is still some debate in the medical community as to the necessity of performing ASCT as primary treatment versus delaying treatment until disease relapse. While improvements in PFS have been shown with immediate ASCT, long-term follow-up has shown no difference in overall survival (OS) or time to second progression. Still, study results suggest that even with effective induction treatment, transplant has a role but can be delayed to time of relapse without compromising OS (Kumar 2021). This means patients have a choice as to the timing of ASCT.

Regardless of whether a patient is transplant eligible or not, the approach to each phase of treatment should be based on individual factors such as features of the disease, patient age, presence of co-morbidities, performance status and personal preferences. Initial treatment for myeloma should:

- Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible [see Module 2]
- Eliminate myeloma cells from the bone marrow (as measured via minimal residual disease [MRD] testing)
- Improve quality of life with as few treatment side effects as possible
- Provide the longest possible period of response before first relapse
- Prolong overall survival (MMRF 2023).

Agents that are toxic to stem cells, such as nitrosoureas or alkylating agents, compromise stem cell reserve. Regimens containing these agents (notably melphalan) should be avoided in patients who are potential candidates for ASCT until stem cells are collected.

It is important to consider supportive care for all patients at the time of diagnosis. Approximately 80 % of patients have bone disease and up to 33 % have renal compromise at the time of presentation. Concomitant problems, such as hypercalcemia, hyperviscosity and coagulation/thrombotic events, should be managed with the appropriate measures prior to initiating treatment. Careful attention to supportive care is critical to avoid early complications that may compromise therapeutic outcome.

Treatment of Newly Diagnosed Transplant Eligible Patients

Newly diagnosed multiple myeloma is typically sensitive to a variety of classes of drugs including:

- Immunomodulatory drugs (IMiDs): e.g., lenalidomide, thalidomide, pomalidomide
- Proteasome inhibitors (Pis): e.g., bortezomib, carfilzomb, ixazomib
- Monoclonal antibodies: e.g., daratumumab, elotuzumab.

Patients with active or symptomatic myeloma and assessed as transplant-eligible are initially treated with first-line treatment, followed by high-dose chemotherapy and ASCT (NCCN 2024). The key treatment goals in otherwise healthy transplant-eligible patients are prolonged survival and depth and duration of response (Mateos 2019).

Most experts and treatment centers recommend a 3-drug regimen as standard first-line treatment in all transplant-eligible patients (**Table 1**). This recommendation is based on improved response rates and depth of response, and longer PFS/OS rates observed with the 3-drug

Table 1. Preferred Regimens for Primary Treatment of Transplant Eligible Patients

Preferred regimens:
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone[a]

Other recommended regimens:
- Daratumumab/lenalidomide/bortezomib/dexamethasone

May be useful in certain circumstances:
- Bortezomib/cyclophosphamide/dexamethasone[b]
- Carfilzomib/cyclophosphamide/dexamethasone
- Bortezomib/doxorubicin/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone [a,b,c]
- Daratumumab/bortezomib/thalidomide/dexamethasone
- Daratumumab/bortezomib/cyclophosphamide/dexamethasone
- Daratumumab/carfilzomib/lenalidomide/dexamethasone[a]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[d] (VTD-PACE)
- Isatuximab-irfc/lenalidomide/bortezomib/dexamethasone

[a] Ixazomib may be substituted for carfilzomib in selected patients; [b] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to proteasome inhibitor (proteasome inhibitor/lenalidomide/dexamethasone). Consider switch to proteasome inhibitor/lenalidomide/dexamethasone after renal function improves; [c] Treatment option for patients with renal insufficiency and/or peripheral neuropathy; [d] Generally reserved for the treatment of aggressive multiple myeloma.
Adapted from: NCCN 2024

regimens. Two-drug treatments (dual treatment) are now discouraged in transplant-eligible patients.

Autologous Stem Cell Transplantation (ASCT)

ASCT involves collecting hematopoietic stem cells from the blood then infusing these cells following a conditioning regimen using chemotherapy with or without radiation treatment (**Figure 1**). For ASCT, the stem cells are obtained from the patient's own peripheral blood. The stem cells are intravenously infused after several cycles of chemotherapy. ASCT results in high response rates and remains the standard of care after primary treatment for eligible patients (NCCN 2024) [Terms relating to hematopoietic stem cell transplant are presented and explained in **Appendix 1**.]

A tandem ASCT (a planned second course of high-dose treatment and ASCT within 6 months of the first course) may be recommended for some patients, especially those with high-risk disease (Mateos 2019). A review of long-term outcomes of ASCT found that tandem ASCT for newly diagnosed multiple myeloma may be superior in extending PFS compared with single ASCT after induction treatment with a bortezomib-based regimen (Petrucci 2016). Repeat ASCT may be considered at the time of disease relapse or as an option for carefully selected patients with progressive disease (NCCN 2024).

Pre-transplant assessment

High-dose chemotherapy followed by ASCT is an established and accepted treatment for newly diagnosed multiple myeloma. Advanced age and renal dysfunction are not absolute contraindications to transplant. Therefore, referral to a transplant center to assess whether a patient is eligible for transplant is important.

Because stem-cell toxin agents, such as nitrosoureas or alkylating agents, compromise stem cell reserve, regimens with these agents (notably melphalan) should be avoided

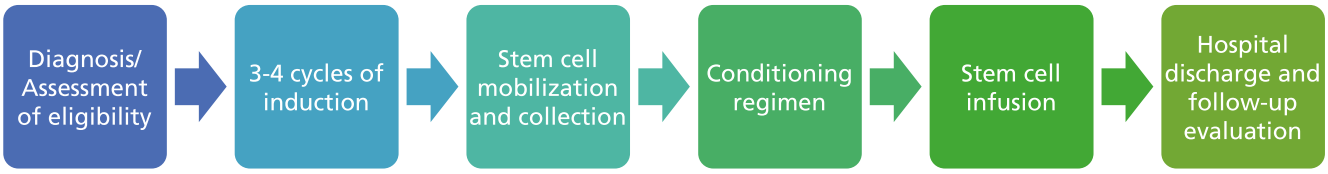

Figure 1. Phases of autologous stem cell transplantation (ASCT). ASCT is a multistep process. After establishing eligibility, patients receive induction treatment. Single or combination agents may be given to mobilize movement of stem cells from bone marrow to peripheral blood. The collection of stem cells can take 4-6 hours and may involve several apheresis sessions to obtain sufficient numbers of cells. Blood counts are at their lowest (nadir) at about 5-10 days after transplantation. Signs of engraftment are usually apparent 10-14 days after transplantation. Myeloma treatment after transplantation may involve a second transplantation or consolidation or maintenance treatment depending on the response. Adapted from: Miceli 2013

Table 2. Induction Regimens for Transplant Eligible Patients	
Regimen	**Anti-neoplastic agents**
Triplet regimens	Bortezomib/lenalidomide/dexamethasone (VRd) Daratumumab/lenalidomide/dexamethasone (DRd)
Quadruplet regimens[a]	Daratumumab/bortezomib/thalidomide/dexamethasone (Dara-VTd) Daratumumab/bortezomib/lenalidomide/dexamethasone (Dara-VRd)
Multi-drug combinations	Anthracycline-containing regimens: Bortezomib, doxorubicin, dexamethasone (PAD) Multi-agent combinations: Bortezomib/dexamethasone/thalidomide/cisplatin/ doxorubicin/cyclophosphamide/etoposide (VDT-PACE)
[a] Quadruplet regimens currently restricted to transplant eligible patients with 2 or 3 high risk factors Adapted from: Rajkumar 2022	

in patients who are potential ASCT candidates until stem cells are collected.

Induction treatment

For transplant eligible patients, the first phase of treatment is induction treatment. Induction treatment is initiated once a confirmed diagnosis of symptomatic multiple myeloma has been established and the patient has been assessed as eligible for ASCT.

Typically, transplant-eligible patients are treated with 4 – 6 cycles of induction treatment prior to harvest of stem cells (Dimopoulos 2021) (**Table 2**). After harvest, patients can either undergo frontline ASCT or resume induction treatment delaying ASCT until first relapse (Rajkumar 2022). The goals of induction are to:

- reduce the myeloma burden
- improve symptoms
- create conditions for successful stem cell collection.

The preferred regimen for induction is bortezomib/lenalidomide/dexamethasone (VRd), which probably offers the best risk:benefit profile among triple drug regimens (NCCN 2024; Dimopoulos 2021). This regimen is associated with improved response rates, depth of response and rates of PFS but has not yet received approval by the European Medicines Agency (EMA). The most commonly used combination regimens for induction treatment in Europe are bortezomib/thalidomide/dexamethasone (VTd) and bortezomib/cyclophosphamide/dexamethasone (VCd) (Mateos 2019).

Clinical evidence from comparison trials of upfront ASCT versus resumption of induction treatment and delay of ASCT until first relapse indicates improvement in PFS with a 3-drug induction regimen followed by stem cell harvest and ASCT (Cavo 2020; Attal 2017; Cavo 2017). Clinical research is lacking to provide evidence that improvement in PFS will also mean improvement in OS. Hence, a delayed ASCT in patients with standard-risk multiple myeloma who prefer such an approach for personal and logistic reasons should be considered (Rajkumar 2022).

The quadruplet-drug regimen (daratumumab/bortezomib/thalidomide/dexamethasone [DaraVTD]) is more efficacious than the 3-drug regimen but data on comparative studies are not yet available. DaraVTD has been approved by EMA and is now the standard induction treatment prior to ASCT. (Of note, thalidomide is rarely used in the US.)

Evidence from the MASTER trial, which compared a combination of four active myeloma agents followed by ASCT, indicates that outcomes for patients with zero or one high-risk abnormality were excellent using a quadruplet induction (Costa 2023). In this trial, a majority of patients achieved MRD negativity and maintained stability without treatment.

Stem cell harvest or collection

Stem cell mobilization is a process in which drugs, such as granulocyte colony stimulating factor (G-CSF), may be used to cause the movement of stem cells from the bone marrow into the blood thus facilitating peripheral stem cell collection. Mobilization of stem cells using chemotherapy, often combined with cytokines, has not been shown to be clearly superior to using growth factor alone.

The collection or harvest of blood stem cells from the peripheral blood system is performed using apheresis and can be initiated in 4 to 5 days or 2 to 4 weeks after mobilization drugs have been administered. During apheresis, blood is drawn from the patient using a machine and spun at high speeds in a centrifugation chamber, which separates the stem cells from blood. The remaining blood components are reinfused. Several apheresis sessions may be required to obtain sufficient numbers of

stem cells and the collected cells may be stored for later use (see EBMT Hematopoietic Stem Cell Mobilization and Apheresis Guide for further information). Harvesting of hematopoietic stem cells in sufficient numbers for at least two transplants in younger patients is recommended.

Conditioning regimen

Conditioning refers to treatment initiated immediately prior to stem cell infusion. This treatment prepares the bone marrow microenvironment to accept the transplanted cells (Garcia 2015). High-dose melphalan (200 mg/m^2) remains the standard conditioning regimen for multiple myeloma (Dimopoulos 2021). Melphalan is associated with severe mucositis, possible cardiotoxicity and, rarely, encephalopathy. The dose of melphalan may be reduced to 100 mg/m^2 - 140 mg/m^2 if the patient is frail or has co-morbidities, or serum creatinine is ≥ -2 mg/dL.

Stem cell infusion

The infusion of stem cells generally occurs 24 to 48 hours after melphalan administration to allow the complete elimination of this agent from the body and avoid cytotoxicity of the infused stem cells. The collected stem cells are infused similar to a blood transfusion.

Engraftment

Stem cell engraftment, or blood count recovery, is the time required for hematopoietic stem cells to migrate from the peripheral blood to the bone marrow and begin to repopulate the bone marrow. Peripheral blood cell lineages recover eight to 40 days after stem cell transplantation, with the absolute neutrophil count reaching a normal level at approximately two to four weeks (Wilton 2023).

Follow-up

The International Myeloma Working Group (IMWG) uniform response criteria are the preferred criteria for determining response to treatment (Kyle 2009). Assessment for treatment response is usually done at 2 to 3 months after ASCT; patients are then followed every 3 to 4 months thereafter. Tests performed at follow-up assessment often include:

- Analysis of serum and/or urine for M-protein
- Serum free light chain assay
- Bone marrow biopsy in patients with no measurable disease
- Assessment of minimal residual disease using multiparametric flow cytometry to identify patients at risk for poorer outcomes (Engelhardt 2014; Shah 2015).

Post-transplant consolidation treatment

Consolidation treatment is a term used for the administration of a short course of treatment, usually with 2 or more drugs, prior to the start of long-term maintenance treatment. Consolidation treatment post ASCT has not been established to date as standard treatment either in the US (Rajkumar 2022) or in Europe (Dimopoulos 2021).

Maintenance treatment

Maintenance treatment is recommended following ASCT and should be considered after completion of 8 to 12 cycles of initial treatment in transplant ineligible patients. Lenalidomide is the standard of care for maintenance treatment for transplant-eligible and transplant-ineligible patients (NCCN 2024). However, there seems to be an increased risk for secondary cancers, especially post-transplantation or following melphalan-containing regimens. Still, meta-analysis results indicate significantly improved PFS and a trend toward OS with lenalidomide maintenance versus no maintenance or placebo (McCarthy 2017). Maintenance with bortezomib plus lenalidomide is often used for patients with high-risk multiple myeloma (Rajkumar 2022). Although there is established evidence to support maintenance treatment, data on optimal duration are lacking.

Allogeneic transplantation

The role of allogeneic and non-myeloablative-allogeneic transplantation in multiple myeloma is controversial. The treatment-related mortality rate and graft-versus-host-disease rates are fairly high with this treatment.

Allogeneic transplantation does not offer OS benefit, even in high-risk disease, compared with tandem ASCT (Dimopoulos 2021).

Treatment of Newly Diagnosed Transplant Ineligible Patients

While treatment options for patients assessed as transplant ineligible were rather limited several years ago, there are now numerous options available providing increasingly better drug response rates. Many regimens for transplant-eligible patients are also appropriate for transplant-ineligible patients such as VRd (preferred regimen) and DRd. Two-drug regimens are recommended for older and/or frail patients.

In Europe, the treatment regimen for patients with symptomatic myeloma who are not eligible for ASCT is based largely on the results of a phase-3 study comparing bortezomib/lenalidomide/dexamethasone (VRd) with lenalidomide/dexamethasone. Study results showed

the superiority of the triplet regimen over the 2-drug regimen on PFS and OS (Durie 2017) and provided the basis for the EMA approval of bortezomib/lenalidomide/dexamethasone for use in transplant ineligible patients (Dimopoulos 2021).

The approval and use of daratumumab added to lenalidomide/dexamethasone (DRd) led to significant improvement in PFS in ineligible transplant patients (Kumar 2020). Specifically, updates of the MAIA clinical trial demonstrated an estimated PFS at 48 months of 60 % with the DRd triplet regimen versus 38 % with the two-drug regimen, lenalidomide/dexamethasone (Kumar 2021).

The NCCN recommendations for treatment regimens for newly diagnosed, transplant-ineligible patients are presented in **Table 3**.

Table 3. Primary Treatment for Transplant Ineligible Patients

Preferred regimens
- Bortezomib/lenalidomide/dexamethasone (VRd)
- Daratumumab/lenalidomide/dexamethasone (DRd)

Other recommended regimens
- Daratumumab/bortezomib/melphalan/prednisone
- Carfilzomib/lenalidomide/dexamethasone
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone

Adapted from: NCCN 2024

Older and frail patients

Multiple myeloma predominantly impacts older adults; the median age at diagnosis is 69 years, 32 % of patients are 65-74 years at diagnosis, and 33 % of patients are 75 years or older (based on SEER data 2016-2020, all races, both sexes) (NCI 2022). Older adults represent a heterogeneous group with wide variations in functional status and overall disease-related outcomes (Nguyen 2021). Not only do outcomes in older patients differ within this group, but they also differ between older and younger patients. For example, while PFS in older patients with myeloma seems to be similar to their younger counterparts, population-based studies have shown little improvement in OS in older patients following the approval of newer treatments (Fiala 2020). Furthermore, real-world populations tend to have poorer outcomes than clinical trial populations and increasing age is associated with a lower likelihood of receiving treatment (Malecek 2018). In a study investigating the type of treatment and outcome of patients over the age of 80, authors found that novel agents produce a similar survival benefit among the oldest patients although the use of any systemic treatment in this group is limited by tolerability (Fiala 2020).

The goal of treating older patients is to avoid undertreating the fit older patient while avoiding overtreating the frail older patient (Fiala 2020). Undertreatment can lead to greater disease burden and overtreatment to extensive sometimes severe toxicities limiting further treatment; either of these scenarios can potentially compromise quality and length of life.

Performing a comprehensive geriatric assessment and, depending on results, an assessment of patient frailty prior to commencing myeloma treatment results in improved tailoring of care and can prevent both over- and undertreatment. In patients aged 65 and older, geriatric assessment should minimally include evaluation of functional status, physical performance and falls, comorbid medical conditions, depression, social activity/support, nutritional status and cognition (Mohile 2018) (**Box 1**). Geriatric assessment is both a diagnostic and therapeutic process that looks at various domains of the older patient and can detect multiple health issues, even in patients with good performance status (Hamaker 2014). Similarly, performing an assessment of the patient's level of frailty can yield information to better stratify and define patients according to their level of fitness and ability to tolerate treatment.

Box 1. Examples of assessment domains for a comprehensive geriatric assessment (CGA)

Functional ability
- Activities of Daily Living (ADL)
  - Katz Activity of Daily Living
- Instrumental Activities of Daily Living (IADL)
  - Lawton Instrumental Activity of Daily Living (IADL)

Physical health
- Screening for disease
- Nutrition
  - Tools: Mini Nutritional Assessment (MNA)
- Vision/hearing
- Urinary continence
- Balance and fall prevention
- Osteoporosis
- Polypharmacy
- Co-morbidities
  - Charlson Comorbidity Index (CCI)
  - Cumulative illness rating scale for geriatrics (CIRS-G)

Cognition and mental health
- Mini Mental State Examination (MMSE) and/or Geriatric Depression Scale (GDS)

Socioenvironmental circumstance

Sources: O'Donovan 2015; Wildiers 2014; Mohile 2018

Frailty is defined as a state of vulnerability to adverse health outcomes when exposed to an external stressor (Ahmed 2007). Although frailty is age-related, advanced chronological age does not equate to frailty, creating

heterogeneity in the aging process. Because few treatment regimens are designed specifically for frail patients, these patients often receive regimens tested on fit older patients that may not be appropriate for their level of physiologic function. Effective treatments in frail patients should be tailored to control the disease while minimizing toxicity and treatment discontinuation: the goal of treatment should be to keep patients asymptomatic as long as possible, preserve functional status and independence, and improve quality of life (Larocca 2015; Mehta 2010). Using a gentler regimen with a better safety profile may provide disease control with less negative impact on quality of life.

Frailty is increasingly being incorporated into multiple myeloma clinical trials. According to results of a systematic review on the prevalence and outcomes of frail older adults entered on clinical trials in multiple myeloma, frailty in 43 studies included in the analysis ranged from 17.2 % to 73.6 % of the cohort (Mian 2023). Compared to non-frail populations, frail patients had worse outcomes: OS at 18 months was 75 % and 89 % and 18-month PFS was 54 % and 68 % in frail versus non-frail patients, respectively.

Several frailty scores have been developed to stratify level of fitness in multiple myeloma patients:

- The International Myeloma Working Group (IMWG) frailty index (Palumbo 2015)
- Revised Myeloma Comorbidity Index (Engelhardt 2017)
- UK Myeloma Research Alliance Myeloma Risk Profile (Cook 2019)
- Eastern Cooperative Oncology Group (EGOC) performance status (https://ecog-acrin.org/resources/ecog-performance-status/)
- Mayo risk score (Milani 2016)
- IFM simplified frailty (Facon 2020)

In real-world practice, ASCT is not necessarily restricted to patients < 65 years and clinicians decide on transplant eligibility based on the individual patient's fitness or frailty level rather than a strict age cut-off. In fact, the number of transplants in older patients has increased in recent years. Two analyses provide support for ASCT in older patients.

This retrospective database analysis of 2092 patients aged ≥ 70 years who had received an ASCT suggested that age at the time of ASCT was not associated with worse PFS although OS was lower in older patients compared with the reference group (those aged 60-69 years). Results suggest that older age should not be a barrier to referral for or performing ASCT (Munshi 2020).

In an exploratory analysis of a large efficacy and toxicity trial of ASCT in older patients (> 65 years), analysis of an age-matched population of patients (transplant eligible and ineligible), showed a significant advantage associated with ASCT with increases in PFS and OS, which persisted after adjustment for baseline covariates including those related to frailty and response to induction. Analysis findings support the use of ASCT for selected fit, older myeloma patients (Pawlyn 2022).

Several approaches to treat older and/or frail patients with multiple myeloma not eligible for high dose chemotherapy with ASCT have been reported. There are myriad new drug combinations for older/frail patients in which the doses of agents are adjusted based on individual tolerance (**Table 4**). Lenalidomide/low-dose dexamethasone, for example, remains an option for older or frail patients (Kumar 2021).

Dexamethasone has been a part of multiple myeloma treatment for almost 40 years. A low-dose dexamethasone schedule of 20 mg on days 1, 8, 15, and 22 of a 28-day cycle and reduced further to 10 mg every 2 to 4 weeks administered alone or followed by lenalidomide for patients older (aged ≥75 years), intermediate fit patients has been shown to be effective with a satisfactory safety profile (Larocca 2021). The use of dexamethasone will probably be considerably reduced or even discontinued in older patients replaced by a combination of lenalidomide and subcutaneous daratumumab in the future (Facon 2024).

Table 4. Novel Treatments for Older, Newly Diagnosed Patients with Multiple Myeloma	
Treatment regimen	**Administration schedule**
Bortezomib/melphalan/prednisone	Nine 6-week cycles
Bortezomib/melphalan/prednisone	Nine 5-week cycles
Bortezomib/cyclophosphamide/dexamethasone	Four 4-week cycles
Daratumumab/bortezomib/melphalan/prednisone	Nine 6-week cycles
Lenalidomide/dexamethasone	4-week cycles until disease progression
Lenalidomide/dexamethasone – lenalidomide	Induction: nine 4-week cycles Maintenance: until disease progression
Bortezomib/lenalidomide/dexamethasone	Induction: eight 3-week cycles Maintenance: 4-week cycles until disease progression
Bortezomib/lenalidomide/dexamethasone lite	Induction: 5-week cycle Consolidation: 6-week cycles
Daratumumab/bortezomib/dexamethasone	Administered until disease progression
Adapted from: Mina 2019	

Patients with co-morbidities

It is estimated that between 55 % and 98 % of older adults (i.e., ≥ 60) experience multimorbidity (Vetrano 2020) and those older adults with cancer experience a higher multimorbidity burden (Williams 2016). The presence of one or more diseases co-occurring with myeloma may affect treatment decisions and was shown to be associated with higher symptom occurrence, severity and distress in older cancer patients (Gaudernack 2021). Several precautions should be undertaken in the presence of common comorbidities (**Table 5**).

A co-morbidity index was developed by physicians at the University of Freiburg to estimate the prognosis and possible treatment-associated risks for patients with myeloma. This easy-to-use assessment is available at: http://www.myelomacomorbidityindex.org/en_calc.html.

Maintenance Treatment

Transplanted patients

The novel agent lenalidomide is being administered soon after ASCT to further improve the quantity and quality of the response. A meta-analysis analyzing over 1200 patients at a median follow-up of 80 months demonstrated a significant 2.5-year benefit in terms of OS with lenalidomide maintenance treatment (McCarthy 2017).

Table 5. Precautions to be taken in the Presence of Common Comorbidities	
Co-morbid condition	**Precautions**
Diabetes	Places patients at risk for hyperglycemia with treatment regimens including steroids: monitor blood sugar levels, adapt hypoglycemic medications to steroid administration; administer high-dose steroids with extreme caution if at all Carefully evaluate any benefit of neuropathic agents in patients with diabetic neuropathy
Cardiac disease	Monitor fluid and electrolyte balance in patients with congestive heart disease or arrhythmias; avoid anthracyclines in patients with decreased ejection fraction; avoid thalidomide in patients with bradycardia; rare but potentially serious cardiac adverse events have been reported with bortezomib
Pulmonary disease	Rare but potentially serious pulmonary adverse events (such as pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome) have been reported with bortezomib. Monitor for cough, shortness of breath, difficulty breathing, change in respiratory status. Report severe shortness of breath to clinical team
Adapted from: Gay 2010	

Table 6: Recommended Regimens for Maintenance Treatment in Transplanted Patients
Preferred regimens: • Lenalidomide
Other recommended regimens: • Bortezomib/lenalidomide
Useful in certain circumstances: • Bortezomib/lenalidomide[a] • Carfilzomib/lenalidomide[a] • Daratumumab +/- lenalidomide[a] • Ixazomib
[a] Dual treatment recommended for high-risk multiple myeloma Adapted from: NCCN 2024

Although maintenance treatment with lenalidomide is associated with more frequent grade 3 or 4 neutropenia and infections, it significantly reduces risk of disease progression or death compared with no maintenance (Palumbo 2014). Lenalidomide treatment is, however, known to cause higher rates of second primary malignancies that occur before myeloma progression (McCarthy 2017).

Despite this risk, lenalidomide is the standard of care (**Table 6**) and the only drug approved by the EMA as monotreatment for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone ASCT (Dimopoulos 2021). The optimal duration of maintenance treatment is still an issue for debate. The benefits of lenalidomide maintenance among patients with high-risk cytogenetics are not clear and these patients may require a different approach. In summary, the benefits of improved PFS with lenalidomide maintenance must be weighed against an increase rate of severe (grade 3 and 4) neutropenia and infections, risk of secondary malignancies and other toxicities; risks and benefits of this treatment should be discussed with patients (NCCN 2024).

Table 7: Recommended Regimens for Maintenance Treatment in Non-transplanted Patients
Preferred regimens: • Lenalidomide
Other recommended regimens: • Bortezomib
Useful in certain circumstances: • Bortezomib/lenalidomide[a] • Ixazomib
[a] Dual treatment recommended for high-risk multiple myeloma Adapted from: NCCN 2024

Non-transplanted patients

The role of maintenance treatment in newly diagnosed transplant-ineligible patients is controversial. While the goal of treatment after induction is to maintain a favorable result, there is no clear consensus as to the length of treatment. The need for and type of maintenance treatment will depend on the individual patient's response to induction treatment (**Table 7**). Most often, approved treatment regimens are continued until progression or unacceptable toxicity occurs.

In older/frail non-transplant eligible patients, the benefit derived from maintenance treatment is questionable. There is now some evidence that lenalidomide-based maintenance treatment in both moderately fit and frail patients provides good outcomes with a good safety profile, underscoring the need to provide personalized treatment according to a patient's frailty status (Bringhen 2020).

Regardless of transplant status, toxicity and treatment burden may limit long-term treatment approaches and drive patient preference for a treatment-free interval. This means that tolerability, limited treatment burden, absence of cumulative or chronic toxicity and limited effect on quality of life are important aspects to consider for maintenance treatment (Dimopoulos 2020). The impact of treatment on patients and their families, such as repeated trips to the hospital or physician appointments, or for intravenous or subcutaneous drug administrations, should be considered when selecting maintenance treatment (Baz 2015).

Treatment of Relapsed and Refractory Multiple Myeloma

There is a high probability of disease relapse after initial disease control. Although new therapeutic agents have led to better disease control, myeloma remains largely incurable and high-risk patients may not benefit from the diverse treatment options (Teoh 2021). For this reason, treatment in patients with recurrent disease usually continues until the next disease progression. Often in cases of relapsed and refractory disease, both physicians and patients are willing to compromise on quality of life and tolerability and choose to accept some toxicities to achieve long-term benefits (Mateos 2019). Although there are no formal definitions for early or late relapse, in practice, relapse occurring within 1 year of the last line of treatment is considered early, whereas those occurring > 1 year after the last treatment are considered later relapses.

Current treatment strategies in relapsed/refractory disease include a change in treatment (relapse occurring in less than 6 months), rechallenge to previous treatment

Table 8. Recommended Regimens for Relapsed/Refractory Disease
Patients who receive second-line treatment: • Second line ASCT for patients who received primary treatment that included ASCT followed by lenalidomide maintenance with an initial remission duration of ≥ 36 months • Patients who received upfront bortezomib-based treatment without lenalidomide or daratumumab should receive lenalidomide/dexamethasone with either carfilzomib, daratumumab, or elotuzumab • Patients who are refractory to upfront lenalidomide could receive pomalidomide/bortezomib/dexamethasone, daratumumab/carfilzomib/dexamethasone (not EMA approved), isatuximab/carfilzomib/dexamethasone or daratumumab/bortezomib/dexamethasone. Patients with t(11;14) who have failed lenalidomide and are protease inhibitor-sensitive may benefit from venetoclax/bortezomib/dexamethasone
Patients at third and subsequent lines of treatment: • Patients with prior exposure to or refractory to both bortezomib and lenalidomide could receive daratumumab/carfilzomib/dexamethasone, isatuximab/pomolidomide/dexamethasone, isatuximab/carfilzomib/dexamethasone, or elotuzumab/pomolidomide/dexamethasone • Patients with t(11;14) refractory to lenalidomide and protease inhibitor-sensitive may be treated with ventoclax/bortezomib/dexamethasone (if available) • Patients who are triple-class refractory, selinexor/dexamethasone or belantamab mafodotin monotreatment is recommended (if available). CAR T cells may be a future option for these patients
ASCT, autologous stem cell transplant; EMA, European Medicines Agency Adapted from: Dimopoulos 2021

regimens (relapse > 6 months), ASCT (progression > 18 months in patients who did not receiving maintenance treatment and after > 36 months in those who received one course of treatment) or enrollment in a clinical trial (Podar 2021). Triple treatment regimens are preferable, although the use of re-induction treatment in these cases is unclear.

In patients for whom a salvage ASCT is not an option, treatment using a lenalidomide/dexamethasone-based regimen and adding, for example, daratumumab, ixazomib or carfilzomib if the patient previously received a bortezomib-based treatment upfront without lenalidomide or daratumumab, should be considered. The regimen daratumumab/lenalidomide/dexamethasone provided a PFS of 83 % at 12 months and 68 % at 24 months in previously treated patients with relapsed and/or refractory disease (Dimopoulos 2016). These results persisted at 3.5 years.

Treatment of relapsed/refractory disease in patients who received 2 or more prior lines of treatment is challenging, especially considering that many of these patients have relapsed while receiving continuous treatment suggesting that their disease is likely refractory to treatment (**Table 8**). Close monitoring may be sufficient for patients with asymptomatic biochemical relapse with slow progression while immediate treatment is required for those with cytogenetic high-risk features and/or with renal or neurologic complications (Podar 2021). Patients whose disease is treatment-refractory to 2 protease inhibitors (e.g., bortezomib or carfilzomib), 2 immunomodulatory drugs (ImiDs) (e.g., thalidomide or lenalidomide), and a CD38 mAb (e.g., daratumumab or isatuximab), have an overall survival of only 5.6 months (Gandhi 2019).

Chimeric antigen receptor (CAR) T-cell treatment to treat multiple myeloma is still being developed. The most widely studied CAR target in myeloma is the B-cell maturation antigen (BCMA). The anti-BCMA CAR T-cell agent idecabtagene vicleucel (ide-cel) has in clinical trials induced early, deep and durable responses (objective response rate [ORR] 82.4 % with a good safety profile) (Wang 2020). Similarly, ciltacabtagene autoleucel (cilta-cel) provided an ORR of 97.9 % with a median duration of response of 21.8 months in previously treated patients with relapsed/refractory myeloma who received at least three prior lines of treatment (Berdeja 2021). Both CAR-T cell agents have received conditional approval by the FDA and EMA regulatory authorities.

Non-anti-BCMA CAR T agents have also been explored for treatment of relapsed/refractory disease, including tisagenlecleucel. For example, CD19-targeted agents in combination with an anti-BCMA active agent are currently being investigated in clinical trials. BCMA-CAR T-cell treatment in combination with known agents for the treatment of myeloma represents a potential new area of research. The outlook for treating relapsed/refractory multiple myeloma, or even newly diagnosed disease, with CAR T-cell treatment appears promising in inducing a sustainable therapeutic effect and may render multiple myeloma a chronic but highly manageable and curable disease (Teoh 2021). While CAR T-cell treatment will potentially become highly specialized, it is associated with very high costs. Challenges to be addressed include defining the optimal use of CAR-T cells, improving persistence of treatment, avoiding antigen loss and reducing potentially serious toxicities such as cytokine release syndrome and neurotoxicity (Moreau 2019).

Multiple Myeloma during Pregnancy

Multiple myeloma, usually considered a disease of older age, is considered a rare occurrence during pregnancy. Cases of multiple myeloma include patients aged 21–43 years diagnosed before conception, during pregnancy and up to 3 months after delivery (Magen 2021). Often, the typical signs and symptoms of multiple myeloma are attributed to pregnancy, delaying the initial diagnosis. Generally, core needle or excisional biopsies and bone marrow biopsies are considered safe procedures to be performed during pregnancy. Computed tomography (CT) scans and positron emission tomography (PET) scans are not advised due to the risk of radiation exposure to the fetus, although with adequate abdominal shielding, plain chest X-ray can be used. The effect of MRI exposure in the prenatal period has not been fully assessed but these should most probably be avoided during the first trimester.

Prompt treatment is advocated in pregnant patients (Mahmoud 2016). Thalidomide, lenalidomide and pomalidomide may induce birth defects and should not be taken by women of child-bearing age. Because of the lack of data on bortezomib use in pregnancy, it too should not be used. Because high-dose corticosteroids present a risk for fetal malformations in the first trimester and a higher risk for obstetric complications in the second or third trimesters, prednisolone is the preferred steroid (Paizis 2019). Should a more intensive combination treatment be required due to more aggressive disease conditions, a pregnancy in the first trimester may need to be terminated. In rapidly progressive cases later in pregnancy, chemotherapy is advisable although standard of care has not been established (Lavi 2014).

The normal physiological changes occurring during pregnancy may influence the pharmacokinetics and pharmacodynamics of chemotherapeutic agents.

Supportive Care

Supportive care involves not only the provision of medications and anti-cancer therapies to manage multiple myeloma symptoms, but it also involves educating patients on the known and potential side effects of each drug, the drug combinations being used and the rationale for the selection of these drugs. Discussions with patients and their caregivers should include information on the availability of supportive care measures, both those that are aimed at preventing, decreasing and managing treatment side effects, such as bone damage, kidney damage and anemia, and those that are intended to address appropriate supportive care for psychological symptoms across the continuum of the cancer experience from diagnosis through treatment to post-treatment thereby enhancing quality of life (Rittenberg 2010).

Table 9. Side Effects of Radiation Treatment to Specific Fields

Radiation field	Potential side effects
Skin	Redness, irritation, swelling, blistering, discoloration Dryness, itchiness, peeling
Head and neck	Mouth sores Swallowing difficulties
Mediastinal area	Nausea Loss of appetite Painful swallowing Cardiac toxicity
Any field	Fatigue

Adapted from: Brigle 2015

While some supportive measures are required for all patients, others address specific problems. More detailed information on supportive care of patients with multiple myeloma is presented in Module 4.

Radiation treatment

Radiation treatment is primarily used for palliation in multiple myeloma and may be used several times during the course of the disease. The traditional indications for radiation treatment are pain control for large osteolytic lesions, prophylactic treatment of impending pathological fractures, post-fracture pain, spinal cord compression and treatment of extramedullary disease (Talamo 2015). In these situations, low-dose radiation is administered to limited fields to limit the effect of irradiation on hematopoietic stem cells or a potential effect on future treatments. Radiation may be administered to patients who are not candidates for systemic treatment or as an adjunct to systemic treatment (Palumbo 2014).

Precise planning in defining the radiation field and radiation technique will help minimize toxicity to the spinal cord, brain, bone marrow and adjacent organs. Radiation fields for cord compression in the thoracic area should be carefully planned to avoid radiation dose exiting into heart structures, which could lead to cardiac toxicity (NCCN 2024) (**Table 9**).

Table 10. Nursing Implications of Agents Commonly used in Treating Multiple Myeloma

Drug/Class/Route	Potential side effects	Management
Bisphosphonate (Pamidronate)[a] IV	Transient pyrexia; hyperalbuminuria; osteonecrosis of the jaw	Pre-treatment dental evaluation after consultation with physician, possibly discontinuing bisphosphonate prior to dental work; regular dental hygiene
Bisphosphonate (Zoledronic acid)[b] IV	Nausea, constipation, vomiting; fatigue; anemia; bone pain; pyrexia; dyspnea; renal adverse effects in patients with renal impairment; osteonecrosis of the jaw	Pre-treatment dental evaluation, regular dental hygiene; Ensure adequate hydration; Monitor GI status
Bortezomib (Velcade)[c] Proteasome inhibitor IV or SQ	Myelosuppression; peripheral neuropathy, neuralgia; nausea, diarrhea, vomiting, constipation; irritation/ erythema at injection site; varicella zoster virus activation; insomnia	Monitor CBC; Monitor for symptoms of myelosuppression & peripheral neuropathy; Monitor GI status; SQ administration and once weekly administration may reduce peripheral neuropathy; Rotate SQ injection sites; Increased risk of varicella zoster virus reactivation: administration of prophylactic acyclovir or valacyclovir recommended
Carfilzomib (Kyprolis)[d] Proteasome inhibitor IV	Anemia, fatigue; diarrhea; dyspnea; neutropenia, thrombocytopenia; pyrexia; headache; upper respiratory infection; hypokalemia; acute renal failure; infusion reactions; tumor lysis syndrome	Monitor CBC; Monitor for symptoms of myelosuppression; Ensure adequate hydration; Inform patients of risk and symptoms of infusion reaction and to notify healthcare professionals if they occur, pre-medicate to reduce severity. Increased risk of varicella zoster virus reactivation: administration of prophylactic acyclovir or valacyclovir recommended
Corticosteroids (dexamethasone, prednisone)	Fatigue, thinning of skin, adrenal insufficiency, hyperglycemia, increased risk of infection, leukocytosis, bone thinning, osteoporosis, mood swings, personality changes, weight gain, decreased libido	Monitor for hyperglycemia/hypoglycemia; Educate patients on side effects including increased infection risk, signs/symptoms of infection and when to contact healthcare professional
Cyclophosphamide Alkylating agent	Cardiac dysfunction (dose-related); nausea/ vomiting; myelosuppression; hemorrhagic cystitis; hyperuricemia; infertility; secondary malignancies	Provide prophylactic antiemetics; monitor for transient ECG changes, dyspnea, tachypnea, fluid retention; encourage fluid intake; educate patient on increased infection risk, signs/ symptoms of infection and preventative measures; monitor for signs/symptoms of TLS; Longer term monitoring for secondary malignancies; refer to fertility health specialist
Daratumumab (Darzalex) Monoclonal antibody	Infusion reactions (uncommon), herpes zoster reactivation; hepatitis B reactivation; myelosuppression;	Educate patients about the risks and symptoms of infusion reaction and to notify healthcare professionals if they occur, pre-medicate to reduce severity; Provide antiviral prophylaxis within one week of starting treatment and continue for 3 months; HBV screening suggested; educate patient on increased infection risk, signs/symptoms of infection and preventative measures;
G-CSF/Filgrastim (Neupogen)[e] Cytokine SQ	Joint, bone pain; elevated WBCs; pyrexia, elevated serum alkaline; headache	Assess and medicate for pain/discomfort
Ixazomib (Ninlaro)[f] Proteasome inhibitor	Thrombocytopenia; GI toxicities; peripheral neuropathy; peripheral edema; cutaneous reactions; thrombotic microangiopathy; hepatotoxicity	Monitor platelet counts at least monthly during treatment; Adjustments in dose may be necessary to decrease/resolve severe diarrhea, constipation, nausea/vomiting; Monitor for symptoms of peripheral neuropathy; Monitor for fluid retention, adjust dosing if necessary; Monitor skin for rash; Monitor skin for signs/symptoms of microangiopathy, discontinue if drug suspected as cause; Monitor hepatitis enzymes during treatment

Table 10. Nursing Implications of Agents Commonly used in Treating Multiple Myeloma

Drug/Class/Route	Potential side effects	Management
Lenalidomide (Revlimid)[g] Immunomodulator	Diarrhea, constipation, nausea; anemia, fatigue, risk of infection due to neutropenia, thrombocytopenia; peripheral edema; insomnia; muscle cramps, spasms, back pain; pyrexia; upper respiratory tract infection; skin rash; dyspnea; dizziness; tremor; thromboembolic event in combination with steroids. May impair stem cell collection in patients who have received > 4-6 cycles.	Monitor CBC; Monitor for symptoms of myelosuppression; Monitor GI status; Anti-thrombosis prophylaxis required (aspirin may be adequate)
Melphalan (Alkeran)[h] Alkylierungsmittel Alkylating agent IV or oral administration	Myelosuppression; nausea, vomiting, diarrhea, oral ulceration; alopecia; renal insufficiency; secondary malignancies	Excreted through the kidneys: caution advised in patients with altered kidney function; Evaluate laboratory parameters before each cycle; Assess CBC for alterations in hematologic status; Consider dose reduction to prevent myelosuppression and increased risk of infection; Suck on ice chips during administration to reduce oral mucositis
Plerixafor (Mozobil)[i] Chemokine inhibitor SQ	In conjunction with G-CSF: diarrhea, nausea, vomiting; fatigue; injection site reactions; headache, arthralgia; dizziness	Monitor GI status, bowel management
Pomalidomide (Pomalyst)[j] Immunomodulator Oral	In combination with steroids: thromboembolic events, myelosuppression, dizziness/confusion, neuropathy. Upper respiratory infection; pyrexia; diarrhea, constipation; back pain; peripheral edema; secondary malignancies; tumor lysis syndrome	Monitor for myelosuppression especially in combination with steroids; monitor GI status; monitor cardiac status; Avoid co-administration with strong CYP1A2 inhibitors
Thalidomide (Thalomid)[k] Immunomodulator Oral	Myelosuppression; thromboembolic events in combination with steroids; hypocalcemia; peripheral neuropathy (late effect); sleepiness, fatigue; constipation, anorexia, nausea; edema	Monitor CBC; Monitor GI status; Thromboembolism prophylaxis (anticoagulation with aspirin or warfarin); Assess for peripheral neuropathy

CBC, complete blood count; GI, gastrointestinal; IV, intravenous; SQ, subcutaneous; WBCs, white blood cells;
Angepasst aus Miceli 2013
[a] Pamidronate 2009; [b] Zoledronic acid 2016; [c] Velcade 2015; [d] Kyprolis 2012; [e] Neupogen 2016; [f] Ninlaro 2022; [g] Revlimid 2015; [h] Alkeran 2008; [i] Mozobil 2015; [j] Pomalyst 2015; [k] Thalomid 2015

Nursing Measures Related to Commonly used Agents in Multiple Myeloma Treatment

Single agents are infrequently used to treat myeloma. The administration of multiple drugs in combination may exacerbate known side effects of individual drugs or cause drug-drug interactions. In regard to any and all medications and chemotherapeutic agents administered, both patients and their caregivers should be provided information on:

- mechanism of action
- route and duration of administration
- possible and expected side effects
- self-care measures (**Table 10**)

Complementary Therapies

Complementary treatment can be defined as therapies used alongside, or integrated with, conventional healthcare (Tavares 2003). By contrast, alternative therapies are generally used in place of conventional treatment. A study conducted in the UK estimated the use of complementary therapies by patients with hematological malignancies including myeloma to be >25 % (Molassiotis 2005a). Complementary treatment has a role in managing myeloma when used as an adjunct to

conventional treatment and can improve quality of life and coping with the effects of the disease (Snowden 2011).

While there is a lack of clinical evidence on complementary treatment in myeloma management, some studies indicate that complementary treatment can help patients to:

- better manage symptoms
- live with altered body image
- promote relaxation
- alleviate anxiety
- reduce anti-cancer treatment side effects
- improve sleep pattern
- reduce stress and tension
- improve well-being (Molassiotis 2005b).

The most commonly used complementary therapies by myeloma patients include acupuncture, homoeopathy, touch therapies (aroma treatment, massage and reflexology), healing and energy therapies (reiki), spiritual healing and therapeutic touch, hypnosis and hypnotherapy, herbal medicines and dietary interventions (Molassiotis 2005a). Yoga and meditation are also frequently used due to their restorative effects. Cannabidiol (CBD) oil may help ease anti-cancer treatment side effects like nausea and vomiting, nerve pain, anxiety, depression, weight loss and insomnia, however, study results are mixed and standardized clinical trials are lacking.

Patients should be asked about their use of any complementary therapy, including herbal teas. Patients, caregivers and healthcare professionals should have access to high-quality information on the role of complementary treatment in myeloma. Further, healthcare professionals should maintain updated information on complementary therapies and carefully consider these therapies before recommending them.

Future Treatment Perspectives

As previously mentioned, CAR T-cell therapies seem to hold promise in the treatment of multiple myeloma. In addition to the various advanced T-cell engineering strategies currently in development, clinical and economic factors should be taken into account for successful incorporation of CAR T cells into existing treatment regimens. More robust and long-term data including evidence of a curative potential is required to solidify the role of this treatment in multiple myeloma (Rodriquez-Lobato 2020).

Bispecific antibodies (BsAbs), novel immunotherapies that simultaneously target and thereby redirect effector immune cells to tumor cells, have shown efficacy in B cell malignancies (Caraccio 2020). Various BsAbs targeting multiple myeloma-specific antigens such as B cell maturation antigen (BCMA) are in pre-clinical and clinical development and have shown effective tumor eradication. In the future, combining BsAbs with immune checkpoint inhibitors may play a key role in advancing myeloma treatment through prevention of T cell exhaustion, which may contribute to both targeted- and immunotherapy resistance and is exacerbated by treatment with BsAbs (Caraccio 2020).

Other interesting areas of current research include the assessment of the role of gut microbiome in shaping the immune system response, including anti-tumor immunity, and the identification of specific biomarkers predictive of treatment response with a patient's heterogeneous multiple myeloma (Gulla 2020).

Greater emphasis is being placed on personalized or tailored treatment. Biomarkers for sensitivity/resistance to particular drugs are under investigation. In the future, therapeutic options may be selected based on the results of serial clonal evaluations, comparing the disease genome at the time of diagnosis and at relapse. The timing and choice of a specific treatment could be important to reduce clonal diversity at diagnosis or at the time of relapse in case of the emergence of a new clone, or, on the contrary, in case of a stable clone that remains sensitive to a former regimen. (Moreau 2013).

To date, most clinical trials exclude older patients. Furthermore, there is a lack of age- and frailty-adapted clinical trials. Real-world validation of randomized trials including older patients could help to identify vulnerabilities present in this population (Gulla 2020).

Resources for Healthcare Professionals, Patients and Caregivers	
American Cancer Society (ACS) www.cancer.org	National non-profit organization providing cancer resources online and community services
American Society for Blood and Marrow Transplantation (ASBMT) www.asbmt.org	International professional association promoting education, clinical standards and research
European Myeloma Network (EMN) myeloma-europe.org.linux9.curanetserver.dk/index.php?index	Supports the development of novel diagnostics and therapies for multiple myeloma
European Oncology Nursing Society (EONS) www.cancernurse.eu	Pan-European organization dedicated to the support and development of cancer nurses
European Society for Blood and Marrow Transplantation (EBMT) www.ebmt.org	European professional association involved in promoting all aspects of transplantation of hematopoietic stem cells
EBMT Handbook https://www.ebmt.org/education/ebmt-handbook	Manual for healthcare professional involved in hematopoietic stem cell transplantation and cellular therapy
European Society for Blood and Marrow Transplantation – Nursing Group www.ebmt.org/Contents/Nursing/Pages/default.aspx	Nursing division aimed at promoting excellence in the provision of blood and marrow transplantation and hematology care
European Society for Blood and Marrow Transplantation – Nursing Group https://www.ebmt.org/ebmt-textbook-nurses	Open access textbook for nurses on hematopoietic stem cell transplantation
International Myeloma Foundation (IMF) www.myeloma.org	Information about myeloma, treatment, research efforts, support available in several languages
International Working Group (IMWG) myeloma.org/PortalPage.action?tabId=8&menuId=125&portalPageId=8	A division of IMF. Conduct basic, clinical and translational research to improve outcomes in myeloma
Multiple Myeloma Research Foundation (MMRF) www.themmrf.org	Information about myeloma, research efforts, support
Myeloma UK www.myeloma.org.uk	Professional and patient information, professional education
National Cancer Institute www.cancer.gov	Information on disease types and research

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Appendix 1: Definitions of Terms Commonly Used in Stem Cell Transplantation

Allogeneic transplant	A procedure in which bone marrow or peripheral blood stem cells from a donor (usually related) are collected, stored and infused into a recipient following high-dose chemotreatment and/or radiation treatment
Autologous transplant	A procedure in which the patient's own bone marrow or peripheral blood stem cells are collected and infused
Collection	Collection or harvesting of stem cells through apheresis. Sessions can last 4 to 6 hours, the number of sessions needed to collect a specified quantity of cells is variable. Collected cells are cryopreserved in DMSO to prevent cell breakdown. Cells may be stored for an indefinite period of time. The dose of peripheral blood stem cells infused is critical to the success and rate of hematopoietic recovery after transplantation.
Conditioning	Chemotherapeutic regimen administered to treat the underlying disease prior to ASCT and prepare the bone marrow microenvironment to accept the transplanted cells. Melphalan 200 mg/m2 is typically used in myeloma
Engraftment	Recovery of blood count, often seen starting 10 days after stem cell infusion. Defined as the first of 3 days with neutrophil count > 0.5 x 10^9/L, platelets > 20 x 10^9/L (without transfusion)
Hematopoietic stem cell	An immature cell that can develop into all types of blood cells, including white blood cells, red blood cells, and platelets. Hematopoietic stem cells are found in the peripheral blood and the bone marrow. Also called blood stem cell.
Induction	Treatment initiated once a confirmed diagnosis of symptomatic multiple myeloma has been established.
Nadir	The lowest point or lowest value of blood cell count; occurs at different times for different cells but usually between day +5 and day +10 after ASCT
Stem cell infusion	Infusion or transplantation of collected stem cells. Infusion time varies depending on the amount of stem cells. The DMSO preservative causes patients to have a distinct odor emanating from the mouth and skin.
Stem cell mobilization	Stimulation and movement of stem cells from the bone marrow into the peripheral blood. Agents used alone or in combination to enhance stem cell mobilization include G-CSF and chemotreatment agents or plerixafor. May take 1-2 weeks depending on agents used.

ASCT, autologous stem cell transplantation; DMSO, dimethyl sulfoxide; G-CSF, granulocyte-colony-stimulating factor
Duarte 2011; Faiman 2013

Quick Facts

- Some commonly used novel therapies as well as multiple myeloma itself can cause peripheral neuropathy, a challenging adverse event that can affect quality of life and compromise optimal treatment.
- Anemia, neutropenia, and thrombocytopenia are expected side effects of novel therapies; patients should be monitored closely and educated about the signs and symptoms of these side effects
- Thromboembolic events or pulmonary embolism are significant side effects of pomalidomide or lenalidomide when these agents are used in combination with corticosteroids or chemotherapy.
- Identification of strategies tailored to address individual patient needs and aimed at preventing a compromise in health-related quality of life is essential to maintaining and improving overall well-being.
- Although individualized care is a core focus of supportive care, it is important to keep in mind that needs and preferences change over time based on perceived health needs, concerns and stage along the cancer trajectory.
- The scope of the impact of symptom experience is extensive in older patients and often affects their quality of life.
- Functional decline is associated with a loss of independence and decreased quality of life; the maintenance of independence, therefore, is a primary goal of interventions for myeloma survivors.
- Caregivers are challenged to assimilate complex information, and to develop skills to provide assistance with activities of daily living as well as activities typically considered to be within the realm of nursing care.

A. Management of the Patient with Multiple Myeloma
    1. Common problems associated with myeloma treatment
    2. Common problems associated with myeloma
        a. Anemia
        b. Bone disease
        c. Renal dysfunction
B. Comorbid Conditions and late effects of treatment
    1. Co-morbid conditions
    2. Late effects of treatment
C. Special Considerations in managing the Older Patient with Multiple Myeloma
D. Psychosocial Issues related to Multiple Myeloma and its Treatment
    1. Quality of life and health-related quality of life
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Management of the Patient with Multiple Myeloma

The treatment of myeloma has dramatically changed in recent years now providing a significant improvement in response and survival rates in comparison to those achieved with previous treatment options. With few exceptions, it is difficult to categorize problems experienced by myeloma patients as being related strictly to the disease or to treatment. Providing the appropriate supportive treatment of these problems is an essential part of the overall management of myeloma.

The type and severity of problems experienced by the patient will vary depending on personal and disease characteristics, the type and duration of administered treatments and the patient's history of adverse events (Kurtin 2016).

One of the challenges in addressing patient problems is reaching and maintaining a balance between alleviation of symptoms and not causing further complications through interventions. For example, safely providing relief of pain through the administration of narcotics while closely monitoring the patient for common side effects of these agents such as constipation and nausea. This means the management of patients with myeloma is complex and multifaceted. The provision of optimal care requires a comprehensive approach, which integrates healthcare professionals from a variety of clinical settings as well as caregivers and patients (Garcia 2015)..

Common problems associated with multiple myeloma treatment

Gastrointestinal (GI) problems are common side effects of myeloma therapy. Some degree of GI toxicity following ASCT is likely to occur and can include:

- oral and gastrointestinal mucositis
- nausea
- vomiting
- diarrhea (Naegele 2018)

Constipation is a common side effect of thalidomide and diarrhea frequently occurs in conjunction with lenalidomide (Faiman, 2016; Gay 2010). Both GI complaints have been reported with bortezomib-based regimens.

Oral mucositis, which results from damage to the mucosal epithelium caused by melphalan administration, can be extremely painful and lead to other problems such as weight loss, anorexia, dehydration and infection (Pallera 2004; Sonis 2004; Brown 2004). Sucking on ice chips or rinsing with ice-cold water (cryotherapy) can effectively prevent oral mucositis caused by high dose melphalan (Al-Rudayni 2021).

Myelosuppression, manifested as a reduction in red blood cells (anemia), white blood cells (neutropenia) and platelets (thrombocytopenia), is a common and expected side effect of agents used in myeloma treatment, occurs following high-dose chemotherapy with melphalan used in the conditioning regimen for autologous stem cell transplantation (ASCT), and as a consequence of the disease itself. The severity of the side effects of anemia, neutropenia and thrombocytopenia will depend on how low the actual blood count of red blood cells, neutrophils and platelets is and the duration of the lowered blood count (**Table 1**).

Fatigue occurs in the majority of patients with myeloma and can be a major cause of reduced functioning and lowered quality of life (Snowden 2011). Unfortunately, fatigue is often under-recognized by healthcare professionals. The causes of fatigue are multifactorial and include treatable causes (i.e., anemia) as well as psychological causes and treatment-related causes.

While an **impaired immune function** is an important characteristic of myeloma that increases the risk of infections, neutropenia, caused by anti-cancer treatment as well as myeloma, also places the patient at risk of developing infection (Kurtin 2016; Gay 2010). Prolonged

Table 1: Severity Grading of Anemia, Neutropenia and Thrombocytopenia

Adverse Event/ Measurement	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life-threatening	Grade 5
Anemia/ Hemoglobin	< LLN – 10 g/dL < LLN – 6.2 mmol/L < LLN – 100 g/L	< 10 – 8 g/dL < 6.2 – 4.9 mmol/L < 100 – 80 g/L	< 8 g/dL < 4.9 mmol/L < 80 g/L	Life-threatening consequences; urgent interventions indicated	Death
Neutropenia/ Neutrophils	< LLN – 1500/mm^3 < LLN – 1.5 x 10^9/L	< 1500 – 1000/mm^3 < 1.5 – 1.0 x 10^9/L	< 1000 – 500/ mm^3 < 1.0 – 0.5 x 10^9/L	< 500/mm^3 < 0.5 x 10^9/L	
Thrombocytopenia/ Platelets	< LLN – 75000/mm^3 < LLN – 75 x 10^9/L	< 75000 – 50000/mm^3 < 75 – 50 x 10^9/L	< 50000 – 25000/mm^3 < 50 – 25 x 10^9/L	< 25000/mm^3 < 25 x 10^9/L	

LLN, lower limit of normal
Source: National Cancer Institute, CTCAE 2017

use of high-dose steroids can compromise host defenses against fungal and viral infections. The risk intensity for infection varies depending on the underlying disease, the myelotoxicity of the agents administered, co-morbidities, age, prior infections and environmental exposure to micro-organisms (Bevans 2009).

Anemia can be caused by myeloma or by treatment whereas neutropenia and thrombocytopenia are more frequently caused by treatment with bortezomib (thrombocytopenia) and lenalidomide and alkylating agents (neutropenia and thrombocytopenia). Anemia and thrombocytopenia are generally treated using transfusion support (**Table 2**). Erythropoiesis-stimulating agents can be used in the treatment of anemia. In patients with a high risk of thromboembolic events including patients previously treated with thalidomide or lenalidomide in combination with doxorubicin and corticosteroids, the use of erythropoiesis-stimulating agents should be carefully reconsidered (Schrijvers 2010). CD38 antibodies (i.e., daratumumab or isatuximab) interfere with routine methods for compatibility testing for blood transfusions. Therefore, phenotyping should be done before CD38 is started (van de Donk 2018).

Osteonecrosis of the jaw, characterized by necrotic-exposed bone in the maxilla-facial region, is uncommon but potentially serious. Risk increases with prolonged bisphosphonate administration or with the administration of the antibody denosumab (**Table 2**). Typical features are pain and localized infection, loosening of teeth and spontaneous avulsion and soft tissue ulceration with sinus formation (Fusco 2022; Snowden 2011). Patients should receive a comprehensive dental examination and appropriate preventive dentistry before beginning bisphosphonate therapy. While on therapy, patients should maintain excellent oral hygiene and avoid invasive dental procedures (Kyle 2007).

Pain is often one of the reasons why patients with myeloma seek medical care (Snowden 2011) and it rarely occurs in isolation of other disease- or treatment-related problems. Most often, pain is accompanied by fatigue and depression. The experience and sensation of pain is highly subjective (**Table 2**). Several measurement tools are available to better assess the location, intensity, type and experience of pain as reported by the patient (Eaton 2009; EONS 2012a; Snowden 2011).

Dermatologic events can be a side effect of treatment with immunomodulators (IMiD). These events are generally mild to moderate and can be easily managed (Gay 2010). In rare cases, more serious toxic epidermic necrolysis and Stevens-Johnson syndrome can occur (Wäsch 2012): both are potentially life-threatening conditions and require specialized interventions. Subcutaneous injection of bortezomib can cause reddening of the skin at the injection site (**Table 2**). The bispecific antibody talquetamab can cause severe skin dryness and hand-foot syndrome, for which creams containing ammonium lactate and Vaseline should be used (Chari 2022).

Thromboembolic events (deep vein thrombosis [DVT], or pulmonary embolism [PE]) are one of the most significant side effects associated with the use of IMiDs (immunomodulatory drugs) such as thalidomide, pomalidomide and lenalidomide, when these agents are used in combination with corticosteroids or chemotherapy (Ludwig 2018). The risk of developing thromboembolic events appears to be increased when erythropoiesis-stimulating agents are added to IMiDs. General risk factors for thromboembolic events include myeloma itself; individual demographics (older age, obesity, immobility); genetic factors (strong family history, blood clotting disorders); co-morbid conditions (cardiac diseases, sickle cell disease); certain procedures; medications (estrogenic agents, antimyeloma therapy) (Terpos 2015; Rome 2008) (**Table 2**).

Cytokine release syndrome (CRS) is associated with the administration of CAR-T cells (chimeric antigen receptor T cells) and treatment with the bispecific antibodies teclistamab and talquetamab. Symptoms of CRS cans range from mild and flu-like to severe and life-threatening. The IL6 antagonist tocilizumab is used to treat CRS. Immune effector cell-associated neurotoxicity syndrome (ICANS) is also associated with CAR T-cell therapy. Symptoms of ICANS are variable and can initially be vague (i.e., mild tremor and confusion, which can progress to agitation, seizures and cerebral edema) (Ellard 2022)

Table 2. Management of Common Treatment-related Problems

Problem	Clinical presentation	Management
Alopecia	Complete loss of hair	Teach patient about cause/duration of alopecia; provide psychosocial support; counsel regarding wig/head protection
Anemia	Fatigue; shortness of breath; chest pain on exertion	Assess for signs/symptoms; provide education on expected occurrence of anemia; erythropoiesis-stimulating agents (administration requires careful consideration); transfusion of packed red blood cells
Anorexia	Weight loss; taste changes; deterioration in general condition; fatigue; nausea, vomiting, diarrhea	Review medications as source of problem; provide oral nutritional supplements, IV hydration; small, frequent meals, calorie counts; weekly weight; nutrition consult; identify and correct underlying cause

Table 2. Management of Common Treatment-related Problems

Problem	Clinical presentation	Management
Constipation	Symptoms can range from occasional/ intermittent decrease in bowel movements to life-threatening consequences (obstruction)	Maintain a high fluid intake and high fiber diet if medically appropriate; increase physical activity; consider laxatives and stimulants
Diarrhea	Increased frequency of bowel movements, loose/watery/soft stools, abdominal cramps, dehydration, weight loss	Review medications as possible cause; If caused by lenalidomide, provide low-fat diet, colesevelam may be beneficial; evaluate electrolyte levels; administer antidiarrheal medication in the absence of GI infection; maintain/increase fluid intake; provide electrolyte replacement; obtain stool specimen for evaluation of enteric pathogens; provide nutritional supplements if indicated
Fatigue	Decrease in energy; inability/difficulty performing activities of daily living; insomnia; not feeling rested after sleeping at night; generalized weakness	Encourage physical activity; evaluate nutritional intake; establish regular sleep/wake periods; advise patient to plan and prioritize daily activities; referral to physical therapy; integrative medicine options (i.e., meditation, yoga and other mindfulness practices that encourage relaxation)
Infection	Fever, chills, myalgia, malaise, nausea, hypotension, hypoxia; assess for sepsis (temperature > 38° C, tachycardia, muscle weakness, fatigue, confusion, drop in blood pressure)	Regularly monitor for signs & symptoms of infection (oral cavity, catheter site); administration of G-CSF until neutrophil recovery; reduce drug dose or discontinue if neutrophil count <500/mm3; infection prophylaxis with antibacterials, antivirals and antifungals; administer broad spectrum antibiotics, acetaminophen, hydration, symptom management
Nausea	Anorexia, weight loss; diminished skin turgor, dehydration	Assess patterns of nausea; determine food intolerances; determine type of nausea (acute, delayed, anticipatory, breakthrough, refractory); may require IV fluids or nutritional support if severe
Oral ulcerations (mucositis)	Soreness, erythema, ulcerations, of oral mucosa; pain; difficulty swallowing	Cryotherapy with high dose melphalan; good and regular oral care; administration of analgesics; dietary consultation
Osteonecrosis of the jaw	Jaw pain, infection, loosening of the teeth,	Good oral care; educate patient about risk; dental care prior to bisphosphonate treatment
Pain	Patient report of new, or a change in existing pain	Routine assessment of pain at all stages of the disease; assess effect of analgesics and modify type of agent and titrate doses to effectiveness; local radiotherapy may provide pain relief; pain specialist consultation if necessary
Peripheral neuropathy	Paresthesia, peripheral pain; sensory deficits; difficulty maintaining balance; weakness	Perform baseline assessment for signs & symptoms of PN; decrease/ discontinue thalidomide if symptoms worsen; treatment of neuropathic pain with medications, acupuncture, massage; consultation with physical therapy; assess risk of falling (particularly in elderly patients); teach patient signs & symptoms of PN and to report early
Skin rash, dry skin	Symptoms generally self-limiting	Antihistamines for symptomatic treatment; assess for potential severe drug reactions
Thrombocytopenia	Mucosal/gastrointestinal bleeding; increased bruising/bleeding, difficulty stopping bleeding; petechiae	Monitor CBC, differential and platelet count; examination of mucous membranes, sclerae, skin; neurologic assessment for symptoms of intracranial bleeding; Advise patient to avoid activities which pose risk of bleeding if platelet count <20,000/mm3
Thromboembolic events (DVT or PE)	DVT: low-grade fever, tachycardia, swelling/ redness of extremity, dull ache/pain/ tight feeling, positive Homan's sign. PE: anxiety, sudden dyspnea, shortness of breath, chest discomfort, tachycardia/ tachypnea, low-grade fever, pleural friction rub	Assess for history/risk for thromboembolic events prior to initiating therapy; thromboprophylaxis using aspirin, LMWH or warfarin; provide education on recognizing signs & symptoms of DVT and PE
Vomiting	Mild (1 episode/24 hours) to more severe (6 episodes/24 hours)	May be self-limiting; offer antiemetic; avoid noxious stimuli; may require IV fluids or nutritional support if severe

CBC, complete blood count; DVT, deep vein thrombosis; G-CSF, granulocyte colony stimulating factor; IV, intravenous; LMWH, low molecular weight heparin; PE, pulmonary embolism; PN, peripheral neuropathy;
References: EONS 2012; Faiman 2014; Garcia 2015; Gay 2010; Kurtin 2016; Ludwig 2018; Rome 2017; Snowden 2011; Tariman 2008; Terpos 2015.

Common problems associated with multiple myeloma

Anemia

Approximately 75 % of patients present with anemia, which is even more frequently seen in patients with recurrent or refractory disease (Gay 2010). Myeloma-related anemia generally improves with disease response to therapy. In cases where the anemia does not improve despite a disease response to treatment, red blood cell transfusions and erythropoiesis-stimulating agents can be considered (Terpos 2015). Studies have shown that erythropoiesis-stimulating agents can increase hemoglobin levels by 2 g/dL or more in 60 % to 75 % of patients with symptomatic anemia (Terpos 2015). The management of disease-related anemia is the same as for treatment-related anemia (**Table 2**).

Bone disease

Approximately 90 % of patients diagnosed with multiple myeloma will develop osteolytic bone lesions during the course of their disease (Bilotti 2011). Pathologic fractures can occur on long bones (upper arm or femur) and on vertebral bodies (**Table 3**). Bone disease associated with myeloma is an important cause of morbidity and mortality (Gay 2010) and can lead to limitations in quality of life and performance status.

A thorough evaluation of bone health should be performed to estimate the risk of skeletal-related events. Bisphosphonate therapy serves as prophylaxis against skeletal events such as hypercalcemia, spinal cord compression, pathologic fracture (Anderson 2018) and should be considered for all patients receiving frontline therapy. EHA and ESMO recommend treating patients with osteolytic bone disease at diagnosis with an antiresorptive agent, i.e., zoledronic acid or denosumab, in addition to specific anti-myeloma therapy (Dimopoulos 2021). Dose adjustments for bisphosphonates are essential in case of renal impairment, both at diagnosis and during treatment (Terpos 2021). Calcium and vitamin D supplementation should be administered to all patients receiving bisphosphonates once serum calcium concentration has returned to normal levels (Terpos 2021).

Supportive measures for bone disease may include the following, as appropriate:

- erythropoietin
- corticosteroids
- surgical intervention
- radiotherapy as a palliative measure for uncontrolled pain, impending pathological fracture or impending spinal cord compression
- plasmapheresis

Renal dysfunction

Renal dysfunction (or impairment) is a serious complication of myeloma, which affects a major subgroup of patients. Mild renal impairment (estimated glomerular filtration < 60 mL/min/1.73m^2) is estimated to occur in at least 25 % to 50 % of patients during the myeloma continuum (Kleber 2009). In addition to disease-related causes, other causes of renal dysfunction are hypercalcemia, hyperuricemia and infections, as well as dehydration and the use of nephrotoxic drugs (aminoglycosides, antibiotics, antihypertensive, lenalidomide-based regimens and non-steroidal anti-inflammatory agents) (**Table 3**).

Fast-acting treatment of multiple myeloma using agents whose known adverse effects do not further impair

Table 3. Management of Common Disease-related Problems

Problem	Clinical presentation	Management
Bone disease	Pathologic fractures of the long bones or vertebral bodies; bone pain	Nebenwirkungen von Bisphosphonaten überwachen (Nierenfunktionsstörungen, GI-Komplikationen, Hyperkalzämie, Osteonekrose des Kiefers), vor der Behandlung Zahnuntersuchung durchführen. Bei drohenden Frakturen oder Rückenmarkskompression: orthopädische Beratung; Sicherheit zu Hause evaluieren; akkurate und dauerhafte Schmerzüberwachung; Schmerz-Management anbieten; Wirbelsäulenunterstützung anbieten, falls angebracht; lastreduzierte Übungen, falls toleriert
Renal dysfunction	Serum creatinine ≥ 2 mg/dL OR creatinine clearance < 30 ml/min OR e-GFR < 60 ml/min (mild dysfunction)	Bei neu diagnostizierten Patienten Thalidomid + Bortezomib oder Lenalidomide starten; erschwerende Faktoren wie Kontrastmittel, nicht-steroide anti-inflammatorische Wirkstoffe, Dehydration vermeiden; Bisphosphonate genau überwachen, adäquate Hydration, Urinalkalisierung sicherstellen, Hyperkalzämie behandeln

e-GFR, estimated glomerular filtration rate GI, gastrointestinal;
Source: Majhail 2017; Terpos 2015

renal function is required to reduce tumor burden and thus improve renal function. Bortezomib, for example, has a rapid onset of action and elimination of the agent is independent of renal clearance so that dose adjustments are not necessary in the presence of renal insufficiency (Terpos 2015). Bortezomib in combination with doxorubicin and dexamethasone was found to result in renal responses in 62 % and complete renal responses (GFR >60 ml/min) in 31 % of patients (Ludwig 2009) and is recommended by the European Myeloma Network (Terpos 2015). Lenalidomide is also a feasible option for treating renal impairment with good response rates, both to disease and recovery of renal function (Terpos 2015).

Comorbid Conditions and Late Effects of Treatment

Comorbid conditions

All patients with comorbidities, such as diabetes, renal insufficiency/failure and cardiopulmonary disease, have a higher risk of infections and should receive antibiotic prophylaxis. Diabetes, cardiac disease and several other co-morbidities can increase the risk of thrombosis and these patients should receive anti-thrombotic prophylaxis. Comorbid conditions may worsen during the cancer survivorship continuum.

Late effects of treatment

Curative intent involves aggressive treatment soon after the diagnosis of multiple myeloma with the primary objective of eradicating the cancer. At this point, the highest priority is to provide treatment that provides the best chance of cure. While long term side effects are not dismissed, they are far less important at the time of diagnosis and deciding primary treatment when a cancer diagnosis poses challenges to mortality. Concerns regarding long term side effects are set aside for if and when they occur, after the cancer itself is treated (Shaw 2021). However, this approach to treatment may not be of relevance or support to patients experiencing sometimes severe and debilitating long term side effects of treatment.

As survival times for patients continue to improve, second primary malignancies have become an increasingly relevant long-term risk for patients with multiple myeloma (**Table 4**) (Poh 2021). While the risk of solid tumors is decreased or not increased, there is a noted increased incidence of hematologic malignancies in this population (Razavi 2013; Chakraborty 2012). Specifically, a higher risk of being diagnosed with acute myeloid leukemia or non-Hodgkin lymphoma has been observed (Poh 2021). Treatment-related risk factors include melphalan and lenalidomide administration and ASCT. However, the benefits of lenalidomide and ASCT on improving outcomes clearly outweigh any risk of secondary malignancies and these treatments should continue to be used (Poh 2021).

In general, the risk of developing hematologic malignancies rises as the duration of follow-up time lengthens: the risk appears to start 12 months after multiple myeloma diagnosis and increases with time, with highest rates usually seen at 5 – 10 years after diagnosis (Costa 2018). Risk factors associated with the development of a second primary malignancy include host-related factors (i.e., sex, age, race/ethnicity, comorbidities, genetic predispositions and disease related-factors), treatment regimen and duration and lifestyle factors known to increase cancer risk (i.e., smoking, sun exposure, obesity) (Khan 2010).

The International Myeloma Working Group highlights the need for increased awareness of secondary malignancies and recommends bone marrow examination at baseline and in the event of any unexplained blood count abnormalities (Musto 2018).

Table 4. Common Late Effects of Cancer Treatment*

System/organ	Complication	General risk factors
Immune system	Infektion	Verlängerte Immunsuppression
Ocular	Cataracts, visual changes, retinopathy Sicca syndrome, xerostomia Microvascular retinopathy	Prolonged corticosteroid use Radiation exposure
Oral	Sicca syndrome, xerostomia Caries	Radiation exposure to head & neck
Pulmonary	Pneumonitis Pulmonary fibrosis Restrictive lung disease	Pre-existing pulmonary disease Radiation exposure to chest/TBI Tobacco use

Table 4. Common Late Effects of Cancer Treatment*

System/organ	Complication	General risk factors
Cardiovascular	Cardiomyopathy Congestive heart failure Arrhythmias Coronary artery disease Thromboembolism	Cumulative dose and combinations of cardiotoxic drugs (anthracyclines) Radiation exposure to chest Older age at transplant Pre-existing cardiovascular risk factors Chronic kidney disease Metabolic syndrome Obesity Longer survival time
Liver	Hepatitis B and C	Cumulative transfusion exposure
Renal and genitourinary	Chronic kidney disease Bladder dysfunction Urinary tract infections Incontinence	Drug exposure (calcineurin inhibitors, amphotericin, aminoglycosides) CMV Hemorrhagic cystitis
Muscle and connective tissue	Myopathy, atrophy Fasciitis/scleroderma Polymyositis	Corticosteroids
Skeletal	Osteonecrosis (joints) Osteoporosis	Pre-existing bone disease Long-term steroid use Inactivity
Nervous system	Peripheral neuropathy Leukoencephalopathy Neuropsychological and cognitive deficits	Radiation exposure to head Exposure to fludarabine Intrathecal chemotherapy
Endocrine	Hypothyroidism Adrenal insufficiency Hypogonadism	Radiation exposure to head & neck Long-term steroid use Stem cell transplantation Radioimmunotherapy Systemic therapies: vascular endothelial growth factor inhibitors, IMiDs, retinoid inhibitors
Second cancers	Solid tumors Hematologic malignancies PTLD	Radiation exposure T-cell depletion Exposure to alkylating agents or etoposides
Psychosocial and sexual	Depression Anxiety Fatigue Sleep disorders Posttraumatic stress disorder Sexual dysfunction, loss of libido	Prior psychiatric disorders Hypogonadism Cancer experience Polyneuropathy
Gonadal	Infertility Treatment-induced menopause Testosterone deficiency	Pelvic radiation High-dose chemotherapy IMiDs Age

*Table content applies to treatments administered for myeloma as well as for other types of cancer.
CMV, cytomegalovirus; IMiD, immunomodulatory agents; PTLD, post-transplant lymphoproliferative disorder; TBI, total body irradiation
Source: Kurtin 2016; Majhail 2017; Morton 2014; Treanor 2014

Special Considerations in Managing the Older Patient with Multiple Myeloma

The burden of treatment in older patients with newly diagnosed multiple myeloma is high within the first year after diagnosis, particularly within the first 3 months (Mian 2021). In one study, factors found by multivariate analysis to be significantly associated with high healthcare burden in the first 12 months were greater comorbidities and poor performance status, along with myeloma-related renal impairment, anemia and bone disease. Regarding treatment, ASCT was associated with a significantly high treatment burden (Mian 2021).

The adverse effects of myeloma and its therapy, such as fatigue, weakness, neurologic compromise, metabolic disturbances, bone loss and pain, may place the older patient at increased risk of falling. The consequences of falling have an additional negative impact on long-term prognosis for older myeloma patients (Bilotti 2011).

Hence, particularly in older patients, it is important to recognize and consider comorbidities. Multimorbidity is associated with a significantly higher symptom burden in older adults, which is subsequently associated with decreased quality of life and increased mortality (Willadsen 2016). In a study evaluating symptom experience of older oncology patients with low versus high levels of multimorbidity before treatment, those with high multimorbidity had significantly higher occurrence rates for feeling nervous, difficulty sleeping, dry mouth and pain. Compared to the low multimorbidity group (mean number 0.5 ±1.5 multimorbidities), the high multimorbidity group (mean number 3.3 ±1.5 multimorbidities) had significantly higher severity ratings for pain, feeling sad, lack of energy, feeling drowsy and worrying (Gaudernack 2021). These study results highlight the scope of the impact of symptom experience in older patients -- the effects on quality of life (QoL) as well as health-related quality of life (HRQoL).

In older myeloma patients, symptoms of comorbidities can mimic symptoms of the disease and/or treatment. Pain from arthritis or osteoporosis, for example, might mimic pain due to bony involvement, peripheral neuropathy commonly seen with diabetes or carpal tunnel syndrome may be difficult to distinguish from peripheral neuropathy secondary to treatment with bortezomib.

Older patients have a higher incidence of adverse events and drug discontinuation. The rate of lenalidomide discontinuation because of adverse events was 24 % with maintenance lenalidomide vs 30 % with continuous lenalidomide-dexamethasone in older, intermediate fit patients (Larocca 2021). In a retrospective study, Mian (2020) found poor adherence in 38 % of newly diagnosed patients over age 65 treated with lenalidomide. These results highlight the need for appropriate and adequate supportive care, including the provision of education on potential side effects of drugs, and early identification of complications and toxicity (Kaweme 2021) as possible interventions to reduce treatment discontinuation.

Therefore, comprehensive management of the older patient with multiple myeloma should be a team effort in which multidisciplinary healthcare specialists from internal medicine, oncology, geriatric oncology, radiology and palliative care working in acute, ambulatory and home care settings are involved to ensure the delivery of quality care that is tailored to the needs of the individual patient.

Psychosocial Issues Related to Multiple Myeloma and its Treatment

Quality of life and health-related quality of life

Patients with multiple myeloma undergoing treatment experience impaired quality of life (QoL) and elevated psychological distress across the disease continuum, regardless of the number of treatments they have received (O'Donnell 2022; Zaleta 2020). Several factors (i.e., age, symptom severity, anemia, disease stage and physical function) can affect QoL, with physical function acting as an important predictor (Robinson 2016). In a study of 16,095 cancer survivors, multiple myeloma patients scored the lowest for both health-related quality of life (HRQoL) and physical functioning (Kent 2015).

Low hemoglobin and albumin levels, severe disease- or treatment-related symptoms, and depression can affect physical function and may, as a consequence, adversely affect QoL (Kim 2019). Psychological late effects may occur as a result of physical late effects such as depression associated with pain (Treanor 2014). Following ASCT, patients often describe feeling "let down" and may express anxiety regarding "what comes next" (Garcia 2015). Symptoms of depression are often overlooked because they sometimes mirror symptoms of cancer treatment. Depression may adversely affect physical health, may increase symptom-related fatigue and distress, and has been associated with a higher incidence of suicide (Garcia 2015).

Effects of treatment for multiple myeloma on cognitive function have been explored. Despite a largely unknown etiology, cognitive impairment occurs during and after cancer treatment and affects QoL in cancer survivors. Changes in cognitive function may not affect an individual's ability to function autonomously to perform activities of daily living but may affect instrumental

activities of daily living such as managing finances, appointments, transportation or shopping (Jekel 2015). In one study, 30 % of patients with multiple myeloma self-reported cancer-related cognitive impairment present at 6 months (Yusuf 2022). By contrast, transplant-ineligible newly diagnosed patients with multiple myeloma demonstrated early and continuous improvements in HRQoL, including improvements in functioning and symptoms, following treatment with daratumumab plus bortezomib/melphalan/prednisone or bortezomib/melphalan/prednisone (Knop 2021).

Of interest, in a study of 289 patients with multiple myeloma across the illness trajectory, 61 % indicated that that were moderately to very seriously concerned about eating and nutrition (Zaleta 2020). This is one of only a handful of studies to assess patient-reported nutrition, a determinant of HRQoL.

Identification of strategies that are tailored to individual patient needs and aimed at preventing a compromise in HRQoL is essential to improving HRQoL. The use of instruments to measure HRQoL and identify deficits has been shown to independently improve HRQOL in general oncology patients (Velikova 2004). The EORTC-QLQ-C30 and its myeloma modules (MY20 and MY24) are the most comprehensively validated instruments for this purpose.

Adherence issues

To achieve maximal benefit from most treatments, patients need to initiate and continue the treatment as prescribed. The reasons for nonadherence are multifactorial and include patient-, physician-, medication and system-related variables (Hershman 2016).
The most common reason for nonadherence is toxicity of the prescribed treatment. Other reasons for nonadherence are the frequency and duration of the treatment, route of administration and patient satisfaction with their medication. The experience of treatment burden can occur if patients are required to travel to a treatment center several times per week over a longer period of time to receive treatment.
Using self-report questionnaires, adherence in patients with multiple myeloma was estimated at 50.5 % (Solano 2021). In this study, one risk factor for medication non-adherence was an Eastern Cooperative Oncology Group Performance Status > 2 and a predictive factor for high medication adherence was high satisfaction with treatment. In a large retrospective study investigating adherence to oral agents, most patients (55.9 %) were adherent (Rutter 2022). Age was the only factor significantly associated with increased adherence: patients between the age of 65 to 73 years and 74 to 79 years were significantly more likely to be adherent when compared to patients < 65 years. Of note, these results on medication adherence in older patients differ from those found in other studies (see above).
While adherence rates were reportedly high in one study of myeloma patients taking an oral chemotherapy regimen (cyclophosphamide, thalidomide and dexamethasone), there was potential for non-intentional nonadherence due to deficits in knowledge of the drug, such as the reason for taking the drug and how to take the drug (Arber 2015) (**Table 5**).

Supportive Care

Myeloma is a chronic disease with no known and effective curative treatment. The disease trajectory involves multiple periods of remission and relapse, and treatment is likely to be administered from the time of diagnosis until the time of death. As functional decline is associated with a loss of independence and decreased QoL, the maintenance of independence is a primary goal for myeloma survivors (Kurtin 2015). Preserving QoL and independent functioning requires maintaining mobility, alleviation of pain, prevention of falls or injuries, optimizing sleep and rest, ensuring adequate nutritional

Table 5. Strategies to Improve Adherence with Oral Anti-Cancer Treatments

Reminder triggers	Pill diaries, pill boxes, patient calendars or spreadsheets, blister packs, cellular phones/alarms, electronic pill bottles, medication electronic monitoring system
Education	Provide education on when and how to take the medication, indications, potential side effects, drug interactions
Interactive e-health interventions	Short message service (SMS) text messages, interactive voice response messages, mobile app
Multidisciplinary team	Coordination of medication adherence care between healthcare professionals
Other interventions	Dose simplification, reduction of patient costs, financial incentives

Adapted from: Pouls 2021; Anderson 2020; Schneider 2011

intake, and the provision of medication support to ease treatment side effects (Kurtin 2016; Kurtin 2017) throughout the trajectory of cancer.

Some of the most common symptoms patients with cancer experience are fatigue, pain, lack of appetite, weight loss, sadness and anxiety. There is evidence, however, that the patient's physical, psychological and social needs across the continuum of the cancer experience are not being met. In the post-treatment phase, components of supportive care, in addition to disease surveillance, that may overcome unmet needs and promote survivors' well-being include psychosocial care, symptom management, health promotion and self-management support (Drury 2017).

Although individualized care is a core focus of supportive care, it is important to keep in mind that needs and preferences fluctuate over time based on perceived health needs, concerns and points of transition in care (Mayo 2021). Based on study results, patients prefer supportive care provided and delivered by a team led by a consultant oncologist. Oncology nurses, primary care and multidisciplinary professionals should be integrated into the team to optimize coordination and impact of supportive care (Mayo 2021).

Caregivers

Both patients and caregivers need to adapt to a diagnosis of myeloma, how it affects the individual patient and what changes in lifestyle will be necessary to successfully manage living with the disease. Caregivers are challenged to assimilate complex information, often very rapidly, and develop skills to provide assistance with activities of daily living, with activities typically considered to be within the realm of nursing care or medical treatment, and to provide emotional support during a difficult period (**Table 6**). Caregivers may be relatives of the patient, friends, acquaintances or volunteers (Kurtin 2013) and their number and presence will vary depending on the patient's condition.

A caregiver plays an essential role in attaining and maintaining optimal outcomes throughout the disease process. While providing support, the caregiver also struggles with her or his own feelings about the diagnosis and the uncertainty about future events and how she or he will cope with them. Healthcare professionals need to understand the role of the caregiver, the dynamics of the caregiver-patient relationship and causes of real and potential caregiver stress (Kurtin 2013).

Self-management in the home setting is becoming increasingly more prevalent as the length of time in hospital decreases. Hence, providing patients and their caregivers with clear instructions on recognizing and managing treatment side effects is important to optimize outcomes.

Caregivers are particularly vulnerable to the high demands of caring for someone with myeloma (Molassiotis 2011). The demands of providing care produce changes in role, emotional well-being, social activities and employment. The level of care required by the patient strongly influences the caregiver's life and, possibly, health effects. Caregivers often require, but do not receive, the respite, health care, psychosocial and financial assistance they need to meet the many needs of the patient.

Providing care is a stressful undertaking; in terms of preventative care, assessment should be made of the degree to which the caregiver's life and health may be negatively affected and recommendations provided on interventions to reduce any negative repercussions of caretaking (Bevans 2012).

Table 6. Key Elements of the Caregiver Role

Direct care activities	Monitor and report treatment side effects Procure and administer medications Make decisions on when to call a healthcare provider Make decisions on administering "as needed" medications Perform technical procedures (dressing changes, IV and pump care)
Indirect care activities	Serve as contact person for healthcare provider Serve as contact person for family, friends Serve as patient advocate Manage household Manage medical and insurance forms and bills Organize transportation
Emotional support	Balance medical expectations while maintaining hope Active listener Provide reassurance, emotional comfort

Adapted from: Kurtin 2013

Interventions to support caregivers:

- Individualize caregiver education
- Provide consistent and clear information, reinforce important concepts
- Provide written material
- Suggest maintaining a diary or log of treatments, blood counts, transfusions and side effects, the treatment administered and the outcome
- Encourage respite from caring for the patient and continuation of hobbies
- Encourage stress management practices such as walking and meditating
- Suggest hospital and community resources to support coping
- Provide criteria and procedure for emergency situations
- Encourage caregiver to seek help and/or assistance if needed

Survivorship

Cancer survivorship is now defined as the period from the time of diagnosis until the end of life (NCI 2016). This may mean that the patient has no signs of cancer after finishing treatment, or the patient is living with, through and beyond cancer – survivorship is different for each patient. The meaning of being a cancer survivor may change over time for the patient.

Cancer survivors may experience social effects relating to their cancer experience such as changes in relationships, and/or employment or financial status (Treanor 2014). They are more likely than the general population to be unemployed and these patients have more difficulty reintegrating into their work life, experience discrimination and disease-associated stigma (Treanor 2014). In fact, an inverse relationship was found between stigmatization and various domains of HRQoL (i.e., isolation, emotional, social and role areas) (Ernst 2017).

An Institute of Medicine report states, "Optimal survivorship care is characterized by an organized plan for follow up that is shared with patients so they can take responsibility for their care" (Hewitt 2006, p. 194). According to this report, the essential components of survivorship care are:

- Prevention and early detection of recurrent cancer
- Surveillance for cancer spread, recurrence or second cancers
- Management of late and long-term disease and treatment side effects
- Coordination between specialists and primary care providers to ensure that all the survivor's health needs are met (Hewitt 2006).

Living while surviving multiple myeloma requires an integration of the most effective therapy to achieve the best and most durable response with the least amount of toxicity (Kurtin 2015). A patient-centered approach is recommended when providing survivorship care and every patient should receive survivorship care. Survivorship care requires a multidisciplinary effort and team approach. Lifestyle interventions aimed at tailored physical activity and nutrition may assist patients to manage their health and perhaps improve their physical functioning, level of experienced fatigue, QoL, psychological distress and long-term health outcomes – all important aspects of cancer survivorship. Practice guidelines that address modifiable lifestyle changes that consider both the length of treatment and the unique disease features of multiple myeloma may support and improve patient QoL and HRQoL and, subsequently, a new normal way of life.

The American Society of Clinical Oncology developed a Cancer Survivorship brochure for patients and their caregivers. Similarly, the American Cancer Society has developed cancer survivorship care guidelines for the care of people with cancer who often experience physical and psychosocial long-term and late effects of cancer and its treatment. These guidelines are intended to help healthcare professionals provide comprehensive clinical follow-up care, including health promotion and care coordination (see Resources).

End of Life Care

It is important that the interdisciplinary team recognize when a patient has advancing and untreatable disease to the point that death is likely to occur within the next several months. In multiple myeloma, this stage of the disease is likely to be evident in the event of a renewed relapse. Discussions with patient and family regarding the right to accept or refuse further medical treatments, or even supportive care, should be followed up with discussions related to the patient's and carer's preferences for any type of future care and where this care should take place. Even as the patient approaches the terminal stage and specific anti-cancer treatments have been withdrawn, blood and platelet transfusions can aid in maintaining quality of life by relieving exertional dyspnea and preventing bleeding (Snowden 2011). Timely referral to a palliative care team and/or hospice will allow for team members to become acquainted with the patient and family even if management of significant symptoms is not immediately needed.

Resources

Professional Organizations	
American Cancer Society (ACS)	Survivorship Care Guidelines for Healthcare Professionals https://www.cancer.org/health-care-professionals/american-cancer-society-survivorship-guidelines.html
European Myeloma Network (EMN)	Guidelines for the management of multiple myeloma-related complications https://www.myeloma-europe.org/publications/european-myeloma-network-guidelines-for-the-management-of-multiple-myeloma-related-complications/?highlight=Guidelines
European Oncology Nursing Society (ONS)	Pan-European organization dedicated to the support and development of cancer nurses. Educational documents: PEP (Putting Evidence into Practice) guidelines available for several topics www.cancernurse.eu
International Myeloma Foundation (IMF) Nurse Leadership Board	Develop and provide broad recommendations for nursing care for myeloma patients https://myeloma.org/PortalPage.action?tabId=8&menuId=201&portalPageId=7
National Cancer Institute (NCI), Division of Cancer Control & Population Sciences, Office of Cancer Survivorship	Information and resources for healthcare professionals, researchers and patients on cancer survivorship https://cancercontrol.cancer.gov
Multinational Association for Supportive Care in Cancer (MASCC)	Teaching Tool for Patients Receiving Oral Agents for Cancer (MOATT) www.mascc.org
Caregiver Information	
Caring for the Caregiver. National Cancer Institute (NCI)	www.cancer.gov/cancertopics/coping/caring-for-the-caregiver
Facing Forward: When Someone You Love Has Completed Cancer Treatment	www.cancer.gov/cancertopics/coping/someone-you-love-completed-cancer-treatment
Caregivers or Care Partners International Myeloma Foundation (IMF)	https://www.myeloma.org/resources-support/caregivers-or-care-partners-myeloma-patients
Family Caregiver Alliance	https://caregiver.org
National Alliance for Caregiving	https://www.caregiving.org
Patient Information	
American Cancer Society, Nutrition and Physical Activity Guidelines for Cancer Survivors	https://www.cancer.org/cancer/risk-prevention/diet-physical-activity/acs-guidelines-nutrition-physical-activity-cancer-prevention/guidelines.html
American Society of Clinical Oncologists (ASCO), Comprehensive information for patients and caregivers	https://www.cancer.net/ https://www.cancer.net/survivorship
Living well with myeloma Myeloma UK	https://www.myeloma.org.uk/me-and-myeloma/living-well/
Myeloma Patients Europe (MPE). An umbrella organization of multiple myeloma patient groups and associations from across Europe. Information is available in several languages.	http://www.mpeurope.org/
National Coalition for Cancer Survivorship (NCCS)	www.canceradvocacy.org
OncoLink OncoLife Survivorship Care Plan	https://oncolife.oncolink.org/
Stupid Cancer	www.stupidcancer.org

Resources

Symptom Assessment Tools

Tool	Source
Peripheral Neuropathy Questionnaire	Colson K, Doss DS, Swift R, Tariman J. Thomas TE. Bortezomib, a newly approved proteasome inhibitor for the treatment of multiple myeloma: nursing implications. Clinical Journal of Oncology Nursing 2004; 8: 473-480
Grading System for Adverse Effects of Cancer Treatment	Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Seminars in Radiation Oncology 2003; 13: 176–181.
Grading System for Mucositis	World Health Organization (WHO) https://www.researchgate.net/figure/264009927_fig2_Table-1-World-Health-Organization-Oral-Mucositis-Assessment-Scale
Oral Mucositis Guidelines	European Oncology Nursing Society. Guidelines incorporate the latest developments in oral mucositis into standardized patient care. http://www.cancernurse.eu/documents/EONSClinicalGuidelinesSection4-en.pdf
Baseline Assessment for Peripheral Neuropathy	European Oncology Nursing Society. Peripheral Neuropathy: Improving symptom management in cancer care through evidence-based practice. Euro PEP (Putting Evidence into Practice) Program. Available in several languages http://www.cancernurse.eu/documents/EONSPEPPeripheralNeuropathyEnglish.pdf
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Scale (neuropathic pain)	http://www.endoexperience.com/documents/Apx4_LANSS.pdf Bennett MI, Attal N, Backonja MM, et al. Using screening tools to identify neuropathic pain.Pain 2007: 127: 199–203
Brief Pain Inventory (short form)	http://www.npcrc.org/files/news/briefpain_short.pdf
National Initiative on Pain Control Pain Assessment Scales	http://www.painedu.org/Downloads/NIPC/Pain%20Assessment%20Scales.pdf
Numeric Pain Intensity Scale	http:// www.partnersagainstpain.com/printouts/A7012AS2.pdf.
Impact of Cancer Scale	Zebrack BJ, Ganz PA, Bernaards CA, Petersen L, Abraham L. Assessing the impact of cancer: development of a new instrument for long-term survivors. Psychooncology. 2006; 15: 407-421
Concerns Checklist	National Cancer Survivorship Initiative- Concerns Checklist; http://www.ncsi.org.uk/wp-content/uploads/MAC13689_Identifyingconcerns_Pad_v3.pdf
Multinational Association for Supportive Care in Cancer (MASCC) (Various tools)	https://mascc.org/resources/assessment-tools/

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Notes

Glossary of Terms*

Term	Abbreviation	Definition
Adjunct therapy		Another treatment used together with the primary treatment intended to assist the primary treatment. Also called adjunctive therapy
Allogeneic stem cell transplantation		A procedure in which a person receives blood-forming stem cells (cells from which all blood cells develop) from a genetically similar, but not identical, donor. This is often a sister or brother, but could be an unrelated donor
Antibody		A molecule (also called an immunoglobulin) produced by a mature B cell (plasma cell) in response to an antigen. When an antibody attaches to an antigen, it helps the body destroy or inactivate the antigen
Antigen		Any substance capable of inducing a specific immune response and reacting with the products of that response; that is, with specific antibody or specifically sensitized T lymphocytes or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulates, such as bacteria and tissue cells.
Apheresis		A process used to collect or harvest blood stem cells from the peripheral blood system prior to stem cell transplantation. Blood is drawn from the patient using a machine, spun at high speeds in a centrifugation chamber, which separates the stem cells from blood. The remaining blood components are reinfused.
Apoptosis		Process of programd cell death
Autologous stem cell transplant	ASCT	A procedure in which blood-forming stem cells (cells from which all blood cells develop) are removed, stored, and later reinfused to the same person after high-dose chemotherapy with/without radiotherapy
B cell or B lymphocyte		A small white blood cell crucial to the immune defenses. B cells come from bone marrow and develop into plasma cells, the source of antibodies
Biomarker		Any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of disease or treatment outcome. Also called molecular marker and signature molecule
Bispecific antibodies		Antibodies with two binding sites directed at two different antigens or two different epitopes on the same antigen
Cancer incidence		The number of new cancers of a specific site/type occurring in a specified population during a year, usually expressed as the number of cancers per 100,000 population at risk
Cancer prevalence		The number of people alive on a certain date who have been diagnosed with cancer. Includes patients newly diagnosed, receiving active treatment, completed treatment, living with progressive disease symptoms
Cancer survivor		An individual is considered a cancer survivor from the time of diagnosis, through the balance of her or his life
Chimeric antigen receptor T cells	CAR T-cell	A therapy in which genetically modified T cells are used to selectively target disease-causing cells
Colony stimulating factors	CSF	A substance that stimulates the production of blood cells. Colony-stimulating factors include granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and promegapoietin
Complete response/ Complete remission	CR	The disappearance of all signs of cancer in response to treatment; does not always mean the cancer has been cured

Term	Abbreviation	Definition
CRAB	CRAB	Criteria used for defining start of treatment for multiple myeloma. C = elevated serum calcium; R = renal insufficiency; A = anemia; B = bone disease. Any one of these factors indicates need for systemic therapy.
Cytokines		Powerful chemical substances secreted by cells enabling cell-to-cell communication. Cytokines include lymphokines produced by lymphocytes and monokines produced by monocytes and macrophages
Cytokine release syndrome		A side effect of CAR T-cell treatment triggered by the activation of T cells on engagement of their CARs or T cell receptors (TCRs) with cognate antigens expressed by tumor cells; activated T cells release cytokines and chemokines
Cytogenetics		A branch of genetics concerned with the study of the structure and function of the cell, especially chromosomes
Cytotoxic T lymphocyte	CTL	Subtype of T cells carrying the CD8 marker, can destroy cells infected by viruses or transformed by cancer
Dendritic cell		An immune cell with highly branched extensions, found in lymphoid tissues; engulfs microbes and stimulates T cells by displaying the foreign antigens of the microbes on surfaces
Fluorescence in situ hybridization	FISH or iFISH	Test that "maps" the genetic material in human cells, including specific genes or portions of genes
Gene expression profiling		The determination of the pattern of genes expressed, at the level of transcription, under specific circumstances or in a specific cell to give a global picture of cellular function
Genomics		The study of genes and their functions and related techniques. Genomics addresses all genes and their inter-relationships to identify their combined influence on the growth and development of the organism
Health-related quality of life	HRQoL	A multi-dimensional concept used to examine the impact of health status on quality of life; considered a useful indicator of overall health
Helper T cells		A subset of T cells carrying the CD4 surface marker, essential for activating antibody production and cytotoxic T cells, and initiating other immune functions
High-dose therapy	HDT	An intensive drug treatment to kill cancer cells, also destroys bone marrow and can cause other severe side effects. HDT usually followed by bone marrow or stem cell transplantation to rebuild the bone marrow
Human leukocyte antigen	HLA	Protein on the surfaces of cells that identifies cells as "self" and performs essential role in immune responses. HLA testing is done to identify tissue matches between donor and recipient
Immune effector cell-associated neurotoxicity syndrome	ICANS	A clinical and neuropsychiatric syndrome that can occur in the days to weeks following administration of certain types of immunotherapy, especially immune effector cell and T cell therapies
ImmunoModuleatory drugs	IMiDs	A therapeutic agent that modifies the immune response or the function of the immune system
Immunoglobulin		One of a family of large protein molecules, or antibodies, produced by mature B cells (plasma cells)

Term	Abbreviation	Definition
Interferon		A biological response modifier; interferes with the division of cancer cells. Types include interferon-alpha, -beta and -gamma. Can be produced in the laboratory and used to treat cancer
Interleukin	IL	One of a group of related proteins made by leukocytes and other cells, a type of cytokine. Provides regulation of immune responses. Can be produced in the laboratory and used as biological response modifier to boost immune system
Interleukin-6	IL-6	An immune protein active in inflammation and B cell maturation; responsible for fever in autoimmune, infectious or non-infectious disease. Interacts with interleukin-6 receptor alpha to induce transcription of inflammatory gene products
Leukocytosis		An increase in the number of white cells in the blood, especially during an infection
M-protein		Abnormal product of antibody-producing plasma cells. Also known as: monoclonal protein, myeloma protein, free immunoglobulin light chains, paraproteins, Bence-Jones proteins, the M spike
Major histocompatibility complex	MHC	A group of genes controlling several aspects of the immune response. MHC genes code for "self" markers on all body cells
Minimal residual disease	MRD	A small number of cancer cells remaining after treatment that cannot be detected by usual scans or tests
Monoclonal gammopathy of undetermined significance	MGUS	A condition in which an abnormal protein, monoclonal protein or M protein produced by plasma cells in bone marrow, is found in blood by electrophoresis and/or immunofixation. May progress to multiple myeloma
Multiple myeloma	MM	Malignant disease of plasma cells
Near complete response	nCR	Response to therapy in which paraprotein is no longer detectable by electrophoresis but by immunofixation
Oncogene		A mutated (changed) form of a gene involved in normal cell growth. Oncogenes may cause the growth of cancer cells. Mutations in genes that become oncogenes can be inherited or caused by exposure to cancer-causing substances in the environment
Opsonization		The process by which bacteria and other cells are altered to become more readily/more efficiently engulfed by phagocytes
Osteoclast-activating factor		A lymphokine that stimulates bone resorption and inhibits bone-collagen synthesis
Osteolysis		The dissolution of bone, especially the loss of calcium from bone
Osteolytic lesion		A "punched out" area of severe bone loss. Also called osteoclastic lesions
Overall survival	OS	The length of time from either the date of diagnosis or the start of treatment during which a patient is still alive
Palliation		The alleviation of symptoms without curing the underlying disease; temporary relief
Pancytopenia		A disorder in which all three cell lines in peripheral blood (red blood cells, white blood cells and platelets) are decreased in number. Usually occurs 10-14 days after marrow ablative therapy

Term	Abbreviation	Definition
Partial response	PR	Treatment outcome where there is a greater than 50 % decrease in M protein; also referred to as partial remission
Progression-free survival	PFS	The length of time during and after cancer treatment that a patient lives with the disease but the cancer does not worsen
Refractory		When a disease or condition does not respond to treatment
Relapse		Return of a disease or signs and symptoms of a disease after a period of improvement
Remission		Period of time when symptoms improve or subside; can be temporary or permanent
Renal response		Positive change in renal function, usually measured by estimated glomerular filtration rate (e-GFR), following treatment
Salvage therapy		Treatment given after the cancer has not responded to other treatments
Serum free light chain assay		Measures levels of free kappa and free lambda light chains which are proteins secreted by plasma cells; used to help detect, diagnose and monitor plasma cell disorders
Smoldering multiple myeloma	SMM	Or asymptomatic myeloma, generally requires close monitoring (active surveillance) but no treatment. Characterized by monoclonal protein and slightly increased numbers of plasma cells in bone marrow
T-cell receptor	TCR	Complex protein molecule on the surfaces of T cells that recognizes bits of foreign antigen bound to self-MHC molecules
Tumor necrosis factor	TNF	A protein produced by white blood cells in response to an antigen or infection, a type of cytokine. Can be produced in the laboratory to boost immune response or cause cell death of some cancer types
Very good partial response	VGPR	Treatment outcome where there is a greater than 90 % decrease in M-protein; also known as very good partial remission.

*The terms listed in this glossary are not necessarily specific to multiple myeloma. Some terms refer to general concepts in the diagnosis, treatment and management of cancers.

Notes

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