



# Concise Review

of the Disease  
and Treatment Options

2018 Edition | Prepared by Brian G.M. Durie, MD



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**Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF's reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.**

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**SUPPORT** The IMF's InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

**ADVOCACY** The IMF's Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community's interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF's Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

**Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.**

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## Introduction

The IMF *Concise Review of the Disease and Treatment Options* is an overview of myeloma, with a discussion of pathophysiology, clinical features, and treatment options. We hope that the information will be helpful to both healthcare professionals and patients.

## What is myeloma?

Myeloma is a cancer of the plasma cells in the bone marrow. Myeloma is synonymous with “multiple myeloma” and “plasma cell myeloma.” The malignant plasma cells, or myeloma cells, accumulate in the bone marrow. The major features of myeloma result from the abnormal accumulation of myeloma cells within the bone marrow, causing:

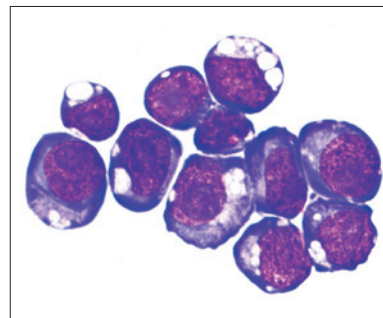
- Disruption of normal bone marrow function reflected by anemia and/or low white counts or platelet counts.
- Destruction and invasion of bone and surrounding areas of bone marrow involvement.
- Production and release of monoclonal protein from the myeloma cells into the blood stream and/or into the urine.
- Reduction of normal immune function, reflected by reduced levels of normal immunoglobulins and increased susceptibility to infection. Infection is also more likely if the white blood cell count is low.

Plasmacytomas are localized tumors composed of plasma cells, which can grow inside bone (intramedullary) or outside bone (extra-medullary or soft-tissue). When there are multiple plasmacytomas inside or outside bone, this condition is also called multiple myeloma. When patients with myeloma have disease outside the bone marrow, this is called extramedullary disease (EMD).

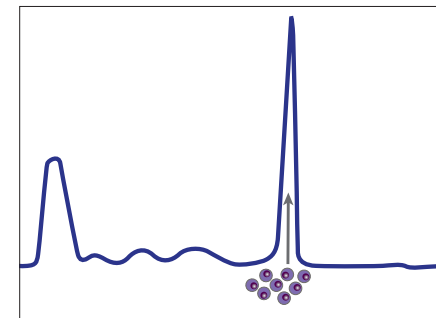
## Production of monoclonal protein by myeloma cells

The characteristic property of myeloma cells is the production and secretion (release) of monoclonal protein into the blood and/or urine. The amount of monoclonal protein produced by myeloma cells varies considerably from patient to patient. In assessing myeloma, it is very important to know if a patient’s myeloma cells are high producers or low producers or non-secretors (with no protein released into the blood or urine). Once the relationship between the protein level and the amount of myeloma in the bone marrow is known, it is possible to interpret and understand the relationship between a particular protein level and the myeloma tumor burden. Monoclonal protein is also called M-protein, M-component, myeloma protein, paraprotein, protein spike, or M-spike.

**Figure 1.** Myeloma cells



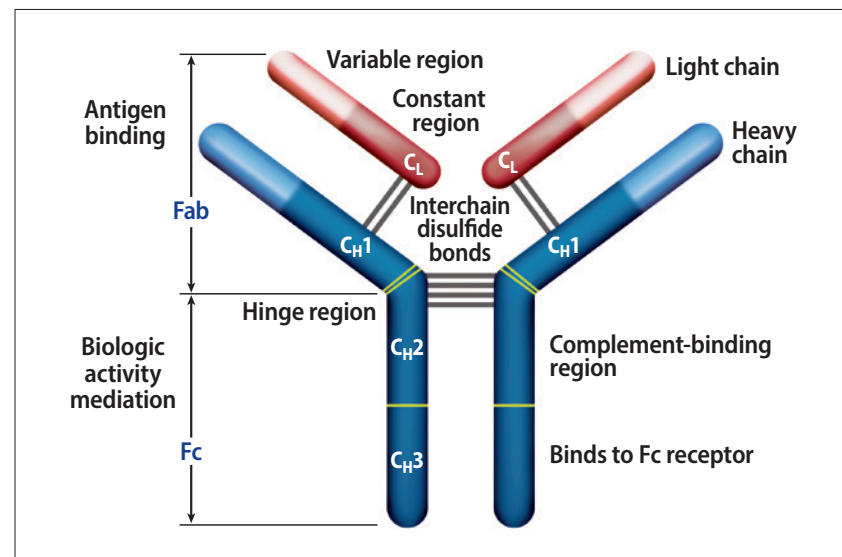
**Figure 2.** Myeloma cells producing M-protein spike



The monoclonal protein is called a spike because of the way it appears on protein electrophoresis, a laboratory technique used to separate and identify proteins.

The **monoclonal protein is an immunoglobulin** or a component/fragment of an immunoglobulin. The structure of a normal immunoglobulin molecule is illustrated in an accompanying Figure. In myeloma cells, mutations have occurred in the genes responsible for immunoglobulin production. Myeloma proteins therefore have an abnormal amino acid sequence and protein structure. Typically, the normal antibody function of the immunoglobulin is lost, and the three-dimensional structure of the molecule may be abnormal.

**Figure 3.** Immunoglobulin molecule structure



Increased production of abnormal immunoglobulin has a number of consequences:

- **Excess monoclonal protein accumulates** in the bloodstream and/or is excreted in the urine.
- **The abnormal monoclonal molecules can adhere** to each other and/or to other tissues such as blood cells, blood vessel walls, and other blood components. This can reduce blood flow and circulation, causing hyperviscosity syndrome (*discussed in text*).
- **More light chains are produced** than are needed to combine with the heavy chains to create a whole immunoglobulin molecule. These excess light chains are called Bence Jones proteins (*see “Annotated history” section*). Free Bence Jones proteins have a molecular weight of 22,000 daltons and are small enough to pass freely into the urine.
- **The abnormal monoclonal proteins can also have a wide range of other properties** including:
  - Binding to normal blood clotting factors, resulting in increased bleeding tendency, enhanced blood clotting, or phlebitis (inflammation of the veins).
  - Binding to nerves to cause neuropathy or to circulating hormones to cause metabolic dysfunction.
- **Free Bence Jones proteins can also adhere** to each other and/or to other tissue (just as the whole immunoglobulin molecule can). In this case the end result is either:
  1. **AL Amyloidosis** – A disease in which the Bence Jones light chains (usually lambda) are cross-linked in a highly symmetric “beta-pleated” fashion and become deposited in tissue around the body, including, for example, kidney, nerves, and heart tissue; or
  2. **Light Chain Deposition Disease (LCDD)** – Light chains (usually kappa) are deposited in a more haphazard fashion, but most selectively in small blood vessels of the eyes and kidneys; or
  3. **Monoclonal Immunoglobulin Deposition Disease (MIDD)** – A disease caused by deposition of fragments of heavy chains, light chains, or both heavy and light chains.

It is important to be aware that routine blood testing can give very strange results because of “stickiness” or hyperviscosity of myeloma blood samples in automated chemical analyzers and/or because of interference with chemical reactions.

**Table 1. Definitions of MGUS and myeloma**

NAME	DEFINITION
<b>Monoclonal Gammopathy of Undetermined Significance (MGUS)</b>	<ul style="list-style-type: none"> <li>• Monoclonal protein present but usually &lt; 3.0 g/dL</li> <li>• No CRAB features or other indicators of active myeloma</li> <li>• Bone marrow monoclonal plasma cells &lt; 10%</li> </ul>
<b>Smoldering Multiple Myeloma (SMM)</b>	<ul style="list-style-type: none"> <li>• Higher level of disease than MGUS: serum M-component can be &gt; 3.0 g/dL and/or bone marrow plasma cells between 10% and 60%, but</li> <li>• No CRAB features or other indicators of active myeloma</li> </ul>
<b>Myeloma based on MDE</b>	<ul style="list-style-type: none"> <li>• &gt; 60% bone marrow plasma cells</li> <li>• Free light chain ratio &gt; 100</li> <li>• &gt; 1 MRI focal lesion</li> </ul>
<b>Myeloma based on CRAB</b>	<ul style="list-style-type: none"> <li>• Monoclonal protein present, and</li> <li>• One or more CRAB features and/or indicators of organ damage*</li> </ul>

\*Organ damage classified as CRAB or any other significant clinical problem linked to myeloma progression such as recurrent infections or neuropathy unrelated to treatment

**C** – calcium elevation (> 10 mg/dL)

**R** – renal dysfunction (creatinine > 2 mg/dL or creatinine clearance < 40 ml/min)

**A** – anemia (hemoglobin < 10 g/dL or > 2g/dL decrease from patient’s normal)

**B** – bone disease (one or more osteolytic lesions detected on skeletal radiography, WBLC CT, or PET/CT)

One or more CRAB features or other significant problem required for diagnosis of Symptomatic Myeloma

## Annotated history

*Dr. Henry Bence Jones was the first to investigate a strange protein in the urine of a patient with myeloma. What caught his attention was a urine protein that dissolved upon boiling, but re-precipitated on cooling: These are called “Bence Jones” light chains. This patient also had a strange bone disease that we now call multiple myeloma. The following is a brief annotated summary of progress in research and treatment for myeloma and related diseases from that time forward.*

### 1844–1850

First case descriptions of myeloma referred to as “mollities and fragilitas ossium” (soft and fragile bones). The first documented patient, Thomas Alexander McBean, was diagnosed in 1845 by W Macintyre in London. The unusual urine problem he discovered was fully investigated by H Bence Jones, who published his

findings in 1848. In 1846, J Dalrymple, a surgeon, determined that the diseased bones contained cells subsequently shown to be plasma cells. W Macintyre published the full details of this case of Bence Jones myeloma in 1850. S Solly published a similar case of myeloma (Sarah Newbury) in 1844, but without any detailed urine studies.

### 1873

J von Rustizky introduced the term “multiple myeloma” to designate the presence of multiple plasma cell lesions in bone.

### 1889

O Kahler published a detailed clinical description of multiple myeloma, “Kahler’s disease.”

### 1890

S Ramon y Cajal provided the first accurate microscopic description of plasma cells.

### 1900

JH Wright discovered that myeloma cells are plasma cells.

### 1903

FP Weber noted that lytic lesions, then known as myeloma bone disease, are detectable using X-rays.

### 1909

FP Weber suggested that plasma cells in the bone marrow cause the myeloma bone destruction.

### 1930s

The routine diagnosis of myeloma remained difficult until the 1930s, when bone marrow aspirates were first used on a larger scale. The development of the ultracentrifuge and serum/urine protein electrophoresis improved both screening and diagnosis.

### 1953

Immunoelectrophoresis allowed exact identification of the monoclonal myeloma proteins. Immunofixation has since been introduced as a more sensitive method.

### 1956

L Korngold and R Lipari noted that Bence Jones proteins are related to normal serum gamma globulin as

well as abnormal serum proteins. In their honor, the two types of Bence Jones proteins are called kappa (κ) and lambda (λ).

### 1958

Discovery of sarcolysin in the USSR. From this, melphalan (Alkeran®) was derived. For the first time, treatment was possible.

### 1961

JG Waldenström emphasized the importance of the differentiation between monoclonal and polyclonal gammopathies. He associated IgM monoclonal proteins with macroglobulinemia as distinct from myeloma.

### 1962

First report of successful treatment of myeloma with melphalan by DE Bergsgael.

### 1964

First report of successful treatment of myeloma with cyclophosphamide (Cytoxan®) by DR Korst. Results with cyclophosphamide proved to be similar to results with melphalan.

### 1969

Melphalan combined with prednisone was shown by R Alexanian to produce better results than melphalan alone.

### 1975

Durie-Salmon Staging System for myeloma introduced. Patients classified to assess benefits of chemotherapy at different disease stages (I, II, III, A or B).

### 1976–1992

Various combinations of chemotherapy agents tried, including the M2 regimen (VBMCP), VMCP-VBAP, and ABCM, with some indication of superiority versus MP. However, in 1992, a comparative meta-analysis (WM Gregory) showed equivalent results for all combinations.

### 1979–1980

Labeling index (growth fraction analysis) first introduced as a test in myeloma and related diseases. Plateau phase of myeloma, defined as stable remission for ≥ 6 months, identified. Plateau phase is a period when the growth fraction (LI%) of residual bone marrow plasma cells is zero.

### 1982

Twin transplants performed by A Fefer and EF Osserman as treatment for myeloma.

### 1983

First use of serum β2 microglobulin as a prognostic test (R Bataille, JA Child, and B Durie).

### 1984

B Barlogie and R Alexanian introduce VAD (vincristine + Adriamycin® + dexamethasone) chemotherapy.

### 1984–1986

First reports of allogeneic transplants in myeloma by various investigators.

### 1986–1996

Large numbers of studies evaluating high-dose therapy with autologous bone marrow or stem cell rescue by various investigators. Both single (TJ McElwain) and double (B Barlogie) transplant procedures introduced.

### 1996

- First randomized study indicating possible benefit of high-dose therapy with bone marrow transplant support versus standard chemotherapy (M Attal on behalf of IFM group).
- Randomized study of the bisphosphonate pamidronate (Aredia®) versus placebo indicates reduction in bone problems (“skeletal related events”).

### 1997

Evidence that viruses may be involved in triggering myeloma. Myeloma more common in patients with HIV and hepatitis C. Human herpes virus-8 (HHV-8) found in bone marrow dendritic cells. RNA found in blood with specificity for SV40 cancer-causing simian (monkey) virus.

### 1998

- Continued research on the role of high-dose chemotherapy with autologous and allogeneic transplant. The magnitude of benefit and patient population(s) likely to benefit remain uncertain. Transplant performed as part of initial (induction) therapy is shown to produce results similar to transplant done at first relapse.
- Chromosome 13 deletions shown to be poor prognostic factor for transplantation as well as some other therapies.
- New study reconfirms prednisone as a helpful maintenance therapy with prolongation of remission. Alpha interferon also shown again to have some benefit in prolonging remission.

### 1999

- Thalidomide shown to be an effective anti-myeloma therapy in patients with relapsing/refractory disease.
- Mini-allogeneic transplant introduced as less toxic method to achieve a graft-versus-myeloma effect.
- Randomized French study shows no major benefit of double autologous transplant versus single transplant.
- Longer-term follow-up shows that Aredia treatment continued for two years is helpful.

### 2000

For the first time, there are several promising new approaches for myeloma therapy. New clinical trials



include thalidomide analogues (e.g., lenalidomide or Revlimid®), long-acting Adriamycin analogues (e.g., pegylated doxorubicin or Doxil®), arsenic trioxide (Trisenox®), anti-angiogenesis agents (e.g., VEGF tyrosine kinase inhibitor), agents to block cell adhesion, and proteasome inhibitors (e.g., bortezomib or Velcade®).

## 2001

New classification system proposed for myeloma and related diseases.

## 2002

- Evidence of efficacy of new agents in clinical trials including Velcade (phase III, Millennium) and Revlimid (phase III, Celgene).
- Thalidomide combined with dexamethasone as frontline therapy for myeloma produces response rate of approximately 70%.
- In the United Kingdom, Medical Research Council (MRC) reports autotransplant results at American Society of Hematology (ASH) annual meeting. Overall benefit noted, especially for patients with high serum  $\beta 2$  microglobulin ( $> 7.5$  mg/L).

## 2003

- Bortezomib (PS-341 or Velcade) is approved in the United States by the Food and Drug Administration (FDA) as treatment for relapsed myeloma following at least two prior therapies.
- MRC autotransplant results provide the second randomized data set indicating benefit of autotransplant versus standard-dose chemotherapy.
- Results of Intergroupe Francophone du Myélome (IFM) study comparing single with double transplant shows overall benefit with the double

transplant after more than four years of follow-up. However, no apparent added benefit is shown for patients already in complete remission with the first transplant.

- Little Rock group (J Shaughnessy/ B Barlogie) shows that bone disease in myeloma is associated with production of a particular protein called DKK-1.

## 2004

- Results of an ECOG randomized trial comparing thalidomide plus dexamethasone versus dexamethasone alone for previously untreated myeloma indicate a 59% response rate with the combination versus 41% with dexamethasone alone (ECOG Criteria).
- Results of a multi-institutional randomized trial comparing Velcade with dexamethasone show superiority of Velcade.
- Early results with Velcade in the frontline setting show excellent results: 83% response rate with Velcade + dexamethasone and 94% with Velcade + Adriamycin + dexamethasone and the ability to harvest stem cells with successful transplantation and engraftment.
- New myeloma staging system introduced, the International Staging System (ISS).

## 2005

- Two large phase III trials show that lenalidomide plus dexamethasone is superior to dexamethasone alone in relapsed myeloma (time to progression  $> 15$  months versus five months).
- Velcade receives full FDA approval for treatment of patients with myeloma after one prior therapy.

- International Staging System (ISS), developed by the International Myeloma Working Group (IMWG) of the International Myeloma Foundation (IMF), is published.
- Numerous new agents in early development.
- Addition of thalidomide to standard melphalan + prednisone regimen shows remarkable added benefit. Several upfront trials are ongoing.

## 2006

- New response criteria for assessing treatment benefit are developed and published.
- Lenalidomide (Revlimid) receives FDA approval for treatment of myeloma in combination with dexamethasone in patients who have received at least one prior therapy.
- Numerous new agents continue to be developed.

## 2007

- FDA accepts a supplemental NDA for use of Velcade plus Doxil to treat relapsed or refractory myeloma in patients who have not previously received Velcade and have received at least one prior therapy.
- Combination thalidomide + dexamethasone plus Doxil compared with thalidomide + dexamethasone in a phase III trial for newly diagnosed myeloma.

## 2008

- Thalidomide approved by the European Medicines Agency (EMA) as part of the MPT regimen (melphalan + prednisone + thalidomide) for frontline therapy.
- Velcade approved by the FDA as part of the VMP regimen (Velcade + melphalan + prednisone) for frontline therapy.

- Many new drugs in development and trials ongoing. The second-generation proteasome inhibitor carfilzomib (PR-171, which later became known by its brand name Kyprolis®) shows promise in early trials.

- FDA approves plerixafor (Mozobil®) in combination with G-CSF for collection of stem cells for autologous transplantation in patients with myeloma.

## 2009

- Development of new drugs continues, including encouraging results from trials of second-generation proteasome inhibitors carfilzomib and NP-0052; HDAC inhibitors vorinostat and panobinostat; HSP-90 disrupter tanesprimycin; monoclonal antibody elotuzumab; and third-generation immunomodulatory drug (IMiD®) pomalidomide (which later became known by its brand name Pomalyst®).
- IMWG analysis shows cytogenetic and FISH abnormalities combined with ISS stage are prognostic; some novel therapies overcome poor risk factors.
- Positive results with CyBorD induction therapy for newly diagnosed myeloma.
- IMWG publishes guidelines for serum free light chain analysis as well as consensus statement and guidelines for imaging techniques in the diagnosis and monitoring of myeloma.
- Several publications by O Landgren support genetic features in pathogenesis of monoclonal gammopathy of undetermined significance (MGUS), and BM Weiss demonstrates that an MGUS precedes myeloma in most patients.

## 2010

- FDA approves a risk evaluation and mitigation strategy (REMS) to ensure the safe use of erythropoiesis-stimulating agents (ESAs), which may promote tumor growth, shorten survival, and increase the risk of cardiovascular adverse events.
- Preliminary identification of erythropoietin (Epo) receptors on myeloma cells.
- Development of new drugs continues, including more encouraging results from trials of second-generation proteasome inhibitor carfilzomib; HDAC inhibitors vorinostat and panobinostat; monoclonal antibody elotuzumab; and third-generation IMiD pomalidomide.
- Several studies suggest a role for lenalidomide maintenance therapy.
- Frontline therapy with novel agents may be as effective as transplantation in eligible patients.
- Zoledronic acid (Zometa®) may have an anti-myeloma effect; effective dental hygiene has reduced occurrence of osteonecrosis of the jaw (ONJ).
- S Rajkumar demonstrates superiority of lenalidomide plus low-dose dexamethasone over lenalidomide plus standard-dose dexamethasone in ECOG E4A03 trial.
- P Richardson publishes positive results with induction therapy for newly diagnosed myeloma with RVD (Revlimid + Velcade + dexamethasone).
- IMWG publishes consensus statement on allogeneic transplant, recommending that it be done for myeloma patients only within the context of a clinical trial.

## 2011

- Approval of subcutaneous (SQ) administration of Velcade based on international phase III trial led by P Moreau (IFM group).
- J San Miguel and O Landgren articulate the need to redefine asymptomatic or smoldering multiple myeloma (SMM) and to treat high-risk SMM.
- A Palumbo publishes new paradigm for the treatment of older patients.
- O Landgren and National Cancer Institute (NCI) team demonstrate higher incidence of MDS and AML among patients with MGUS.
- CAFE study demonstrates that balloon kyphoplasty is superior to non-surgical approaches in management of painful vertebral compression fractures.
- Complete response (CR) after stem cell transplant determined to be a “central prognostic factor” by Spanish Myeloma Group (GEMM).
- Italian group demonstrates correlation of CR with long-term PFS and OS in elderly patients treated with novel agents.
- IMWG publishes guidelines for the treatment of patients who are candidates for autologous stem cell transplant.

## 2012

- Carfilzomib (Kyprolis) receives FDA approval for the treatment of patients with myeloma who have had at least two prior therapies, including bortezomib and an IMiD, and demonstrated disease progression on or within 60 days of the last therapy.
- IMWG publishes data on progression and survival after treatment with IMiDs and bortezomib, and

establishes a benchmark of 9-month median OS.

- IMWG publishes consensus statement on plasma cell leukemia, including diagnostic requirements, response criteria, and treatment recommendations.
- 4-drug EVOLUTION study with bortezomib, dexamethasone, cyclophosphamide, and lenalidomide demonstrates no benefit and more toxicity than 3-drug regimens VCD and VRD.
- M Faham presents paper on detection of circulating myeloma cells in the peripheral blood of 93% of the patients tested with high-throughput sequencing of DNA and RNA.
- Studies of carfilzomib in combination therapies (KCyD, KRd, KTD, KCyTD) and of pomalidomide in combination therapies (Pd, PKD, PCyPred, BiaxinPD, PCyD, PVDd) demonstrate their efficacy as “platform” drugs.
- First studies of oral proteasome inhibitors, MLN9708 (ixazomib) and ONX0912 (oprozomib).
- First studies of anti-CD 38 monoclonal antibody, daratumumab, demonstrate single-agent activity.

## 2013

- Pomalidomide (Pomalyst) receives FDA approval for patients with myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.
- First studies presented of anti-CD monoclonal antibody, SAR650984, demonstrate single-agent activity.
- MV Mateos et al. publish results of trial comparing lenalidomide plus

dexamethasone versus observation in high-risk SMM. Time to progression (TTP) and overall survival (OS) significantly longer in the lenalidomide + dexamethasone arm.

- IFM’s FIRST trial demonstrates superiority of continuous lenalidomide + dexamethasone over MPT or lenalidomide + dexamethasone for 18 months, laying the groundwork for later EMA approval of frontline lenalidomide.
- Combination of bortezomib, dexamethasone, and HDAC inhibitor panobinostat for relapsed/refractory myeloma improves progression-free survival over bortezomib + dexamethasone.
- Two studies determine that progression of SMM to active disease is significantly different based on the underlying cytogenetic subtype of the disease.
- B Paiva et al. publish an immunophenotypic algorithm to identify newly diagnosed myeloma with an MGUS-like signature and long-term disease control.
- A Dispenzieri et al. reclassify highest-risk SMM as active myeloma requiring treatment.

## 2014

- A Palumbo publishes meta-analysis of second primary malignancies with lenalidomide therapy and identifies increased risk with combination of melphalan + lenalidomide, but not with lenalidomide + cyclophosphamide or lenalidomide + dexamethasone.
- MT Drake et al. find that cortical bone microarchitecture is weakened in MGUS patients compared to age-matched controls.

- New methods of minimal residual disease (MRD) detection by multi-parameter flow cytometry and deep sequencing provide higher sensitivity in quantifying response to treatment.
- A Palumbo et al. determine that continuous therapy improves PFS1, PFS2, and OS over fixed-duration therapy.
- Hevlyte® test approved by FDA for use in IgA and IgG myeloma.
- SJ Russell publishes proof of principle on systemic oncolytic virotherapy with measles virus.
- IMWG publishes updated criteria for the diagnosis of myeloma, defining ultra-high-risk SMM as myeloma.

## 2015

- FDA and EMA approve lenalidomide (Revlimid) in the frontline setting based on the FIRST trial, with caveats about harvesting stem cells after only four cycles of therapy, careful monitoring of blood counts, and risk of SPMs in the post-transplant setting.
- IMWG publishes report on geriatric assessment tool developed by A Palumbo et al.
- IMWG publishes consensus statement on the role of MRI in the management of patients with myeloma.
- IMWG publishes consensus recommendations for the uniform reporting of clinical trials.
- IMWG publishes revised International Staging System (R-ISS) for myeloma.
- IMWG jointly publishes consensus statement on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma (with ASBMT, ESBMT, and BMTCTN).

- FDA approves panobinostat (Farydak®) in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an IMiD.
- In November, FDA approves three new drugs for the treatment of relapsed disease: daratumumab (Darzalex®), the first monoclonal antibody for the treatment of myeloma, followed by ixazomib (Ninlaro®), the first oral proteasome inhibitor, and elotuzumab (Empliciti®), an immunostimulatory monoclonal antibody. Both of the latter are indicated in combination with lenalidomide and dexamethasone.

## 2016

- IMWG publishes *Gene signature combinations improve prognostic stratification of multiple myeloma patients*.
- IMWG publishes *Recommendations for management of relapsed multiple myeloma*.
- IMWG publishes *Recommendations for the diagnosis and management of myeloma-related renal impairment*.
- IMWG publishes *Consensus criteria for response and minimal residual disease assessment in multiple myeloma*.
- In October, sponsored by the IMF's Black Swan Research Initiative® (BSRI®), the iStopMM® study launches in Iceland under the direction of principal investigator S Kristinsson. All consenting citizens over the age of 40 (approximately 140,000 people) are screened for MGUS, SMM, and myeloma. Those with myeloma are treated; those with MGUS and SMM are monitored and invited to participate in a randomized clinical trial to prevent the onset of myeloma.

- In November, FDA approves daratumumab in combination with lenalidomide + dexamethasone (based on the POLLUX study) or in combination with bortezomib + dexamethasone (based on the CASTOR study) for the treatment of patients who have had at least one prior therapy.
- BMT CTN StaMINA study presented at ASH demonstrates equal PFS and OS at 38 months follow-up for each of three approaches to upfront transplant: (1) ASCT followed by lenalidomide maintenance, (2) tandem ASCT followed by lenalidomide maintenance, and (3) ASCT plus four cycles of VRD consolidation followed by lenalidomide maintenance.

## 2017

- B Durie et al. publish results of the randomized phase III SWOG 0777 clinical trial in *Lancet*, comparing VRD to RD in newly diagnosed myeloma patients ineligible for ASCT. Study demonstrates superiority of triplet therapy combining a proteasome inhibitor and an immunomodulatory agent.
- FDA approves lenalidomide as maintenance therapy after autologous stem cell transplant in newly diagnosed myeloma patients.
- FDA approves daratumumab in combination with pomalidomide and dexamethasone for the treatment of myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- IMWG publishes consensus statement on the role of <sup>18</sup>F-FDG PET/CT in the diagnosis and management of myeloma and other plasma cell disorders.

- IMWG publishes an overview and consensus on second primary malignancies in myeloma.
- IMWG publishes a study on the natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors.
- M Attal publishes the final results of the IFM 2009 clinical trial, which demonstrated that although PFS and MRD-negative rates were improved with RVD and upfront transplant, overall survival at 4 years did not differ significantly between the transplantation group and the RVD-alone group.
- Spanish PETHEMA/GEM cooperative study group publishes *Prognostic value of antigen expression in multiple myeloma*, characterizing the phenotypic profile of tumor cells found during NGF MRD testing in patients with minimal residual disease.

## 2018

- FDA and EMA approve denosumab (Xgeva®) for the prevention of skeletal-related events in patients with myeloma.
- FDA approves daratumumab (Darzalex) in combination with VMP for the treatment of patients with newly diagnosed myeloma who are ineligible for autologous stem cell transplant based on the results of the phase III ALCYONE clinical trial conducted in Europe and published in *NEJM* in February 2018.
- FDA grants breakthrough status to selinexor based on phase IIb data demonstrating 24.5% ORR, 4.4 months median PFS, and manageable safety profile in patients with penta-refractory myeloma.



## Epidemiology

Currently, there are approximately 750,000 people living with myeloma worldwide, with approximately 180,000 in the United States. The American Cancer Society estimates that 30,770 Americans will be diagnosed with myeloma in 2018 (16,400 men and 14,370 women). The incidence of myeloma rises with age. Myeloma is most frequently diagnosed in individuals who are 65 to 74 years old, but it is now also being diagnosed in people younger than 50. Only 5%–10% of myeloma patients are under the age of 40. Myeloma in children has been reported, but it is extremely rare.

Men are more likely than women to develop myeloma. The disease is twice as common in people of African descent. It appears that the incidence of myeloma is increasing in several parts of the world, especially in Asia. The incidence of myeloma varies from country to country from a low of 1/100,000 in China to approximately 4/100,000 in most industrialized Western countries. Better diagnostic techniques and the higher average age of the general population may, in part, explain the rising incidence over the last several decades. A trend toward more frequent myeloma in patients under age 55 implies important environmental causative factors arising in the past 60 years.

Several recent studies have evaluated the causation of, or predisposition to, myeloma, MGUS, and related disorders. Environmental or work-related exposure to toxic chemicals are definite causal factors. Firefighters, other first responders, and individuals in a variety of occupations with toxic exposure such as farmers and farm workers, as well as individuals who

are obese, are at increased risk of myeloma. Eating seafood contaminated with heavy metals and/or chemicals may be another risk factor for myeloma. Other medical conditions including immune system disorders and infections can be underlying and/or trigger factors. Several studies are focused on the genetic risk factors for myeloma.

## Pathophysiology

The uncontrolled growth of myeloma cells has many consequences, including:

- skeletal destruction;
- bone marrow failure;
- increased plasma volume and viscosity;
- suppression of normal immunoglobulin production;
- renal insufficiency.

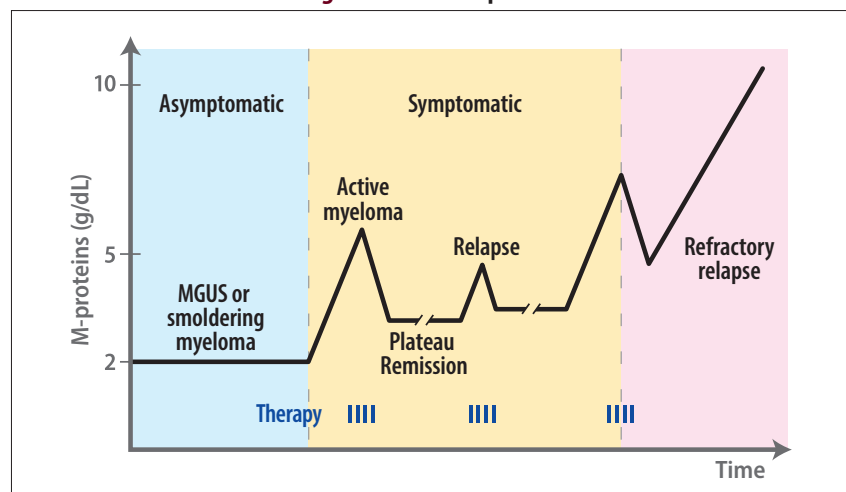
Nonetheless, the disease can be asymptomatic for many years, as noted in the discussion of MGUS. In the symptomatic phase, the most common presenting complaint among myeloma patients is bone pain. The serum and/or urine M-protein is elevated and typically rising at the time of diagnosis. (Please note: “M” is used for Monoclonal, Myeloma, Monoclonal immunoglobulin, and M-component. These are not quite identical, but are used synonymously.) The overall pattern of disease phases for myeloma patients is illustrated in the accompanying Figure. It is important to note that there can be multiple periods of response and remission. The pathophysiology of myeloma is summarized in schematic form in the accompanying Table.

## Bone disease

Ever since the first recognition of myeloma in 1844, there has been awareness of an unusual and unique type of bone disease. It has taken until quite recently to determine the mechanisms involved. The first clue was that both myeloma cells and increased numbers of osteoclasts are present at sites of bone destruction. Understanding of the mechanisms of bone destruction has evolved from the following factors:

- The observation that myeloma cells produce osteoclast-activating factors (OAFs).
- The identification of local cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  and - $\beta$ ; chemokines such as MIP- $\alpha$ ; and cell-cell adhesion processes involving  $\beta$ 3 integrin, all of which are involved in producing increased numbers and activity of osteoclasts.
- The identification of a substance called RANK ligand (RANKL) as a critical mediator of osteoclast activation.

**Figure 4. Disease phases**



Many details of the mechanisms of bone disease in myeloma are now understood. Several targets for treatment approaches have been identified.

Besides the activation of osteoclasts, the other characteristic feature of myeloma bone disease is the inhibition of osteoblasts, which are responsible for new bone production and bone healing. “Coupling” between osteoclast and osteoblast function is responsible for normal bone remodeling and repair. The mechanisms responsible for “un-coupling” in myeloma are under investigation. An important new observation is that the cholesterol-lowering statins (HMG-CoA reductase inhibitors) can enhance osteoblast activity and promote bone healing. Both bortezomib and lenalidomide have been shown to promote bone healing in addition to exerting potent anti-myeloma activity. Studies to further investigate the benefit of several new bone therapies are ongoing.

## Anemia

Anemia is a characteristic feature of myeloma. Although simple physical displacement of marrow red blood cell precursors is undoubtedly a factor, the specific inhibition of red cell production by micro-environmental cytokines and adhesion molecules is a more functional explanation. Two research teams have described the involvement of hepcidin (a peptide hormone that controls iron regulation) in anemia caused by myeloma. Their research was based on the hypothesis that interleukin-6 (IL-6) and certain bone morphogenetic proteins (BMPs), cytokines produced in myeloma, are also known to be regulators of hepcidin. Improvement in anemia thus occurs with successful treatment of the myeloma. Recombinant epoietin alpha should be used with caution, as reports have noted the association of epoietin with increased tumor growth and reduced survival in cancer patients, and the identification of epoietin receptors on myeloma cells.

## Kidney dysfunction

Impairment of kidney function is a common complication in patients with myeloma. However, not every patient will have this problem. In some patients, myeloma proteins (especially Bence Jones light chains) cause renal injury by a variety of mechanisms ranging from tubular damage resulting from large accumulations of precipitated light chains, to effects of myeloma proteins deposited as amyloid, to selective tubular damage resulting in the metabolic effects of an entity called Fanconi syndrome. Fanconi syndrome is a type of selective kidney tubular damage with leakage of amino acids and phosphates into the urine, which can in turn cause metabolic bone disease.

**Table 2. Schema of pathophysiology**

<b>Skeletal Findings</b>		
• Solitary or multiple osteolytic lesions	• Diffuse osteoporosis (osteopenia)	
<b>Associated Effects of Bone Destruction</b>		
• Elevated serum calcium	• Hypercaliuria (calcium increase in urine)	
• Bone fractures	• Loss of height (vertebral collapse)	
<b>Extramedullary (extraskelatal) Myeloma</b>		
Soft tissue involvement, mostly common in head/neck area (e.g., nasopharynx); also in liver, kidney, and other soft tissue sites including skin		
<b>Peripheral Blood</b>		
• Anemia	• Thrombocytopenia	• Circulating monoclonal B lymphocytes (precursors of myeloma cells)
• Abnormal clotting	• Plasma cell leukemia	
• Leukopenia	• Circulating plasma cells	
<b>Plasma Protein Changes</b>		
• Hyperproteinemia (elevated protein)	• Narrowed anion gap (low serum sodium)	
• Hypervolemia (expanded volume)	• Elevated serum $\beta$ 2-microglobulin	
• Monoclonal immunoglobulins (IgG, IgA, IgD, IgE, IgM or light chains only)	• Decreased serum albumin	
	• Elevated serum IL-6 and C-reactive protein (CRP)	
<b>Kidney Abnormalities</b>		
• Proteinuria, casts without leukocytes or erythrocytes	• Uremia (kidney failure)	
• Tubular dysfunction with acidosis (Fanconi syndrome)	• Amyloidosis or light chain deposition disease and renal dysfunction	

Other important factors related to kidney dysfunction in myeloma patients include increased levels of calcium and/or uric acid, infection, and the effects of drugs such as nephrotoxic antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), or contrast agents or dyes used for diagnostic studies. Gadolinium-based contrast agents used with MRI have a potentially toxic effect. Patients with kidney problems should discuss the use of gadolinium with their physicians. Awareness of potential kidney damage and maintenance of sufficient fluid intake are especially important for patients with myeloma to help avert the damaging effects of these various factors.

## Other organ dysfunction

Myeloma cells can accumulate in bone marrow and/or in a variety of tissue sites and produce a broad range of potential complications, including the following:

■ **Neurologic effects** – Nerve tissue is often affected in myeloma patients either by the direct antibody effects of myeloma proteins against nerves (e.g., myelin sheaths) or by deposition of amyloid fibrils on nerves, thus impairing function. These effects result in peripheral neuropathies that must be distinguished from other causes of neuropathy, such as diabetes mellitus, or from primary nerve disorders, such as multiple sclerosis, Parkinson’s disease, and others. Because of myeloma patients’ susceptibility to infection, viral infections of nerve tissue are quite common, most particularly varicella zoster (shingles), herpes zoster (cold sores), Epstein-Barr virus (mononucleosis), or cytomegalovirus, which may result in Bell’s Palsy (partial facial paralysis) or other complications.

■ **Plasmacytomas** – Both in bone and in soft tissue, plasmacytomas can result in compression or displacement of nerves, the spinal cord, or even brain tissue. These pressure effects often represent a medical emergency that requires immediate treatment with high doses of corticosteroids, radiation therapy, or neurosurgery.

■ **Infections** – The predisposition to infections is perhaps the single most characteristic feature of myeloma patients besides the strong tendency for bone disease. The mechanisms responsible for infection susceptibility are not fully understood. The presence of active myeloma in the bone marrow results in impairment of normal immune function, including inhibition of normal antibody production (reflected by hypogammaglobulinemia), impaired T lymphocyte function, and activated yet aberrant monocyte/macrophage function. Some studies indicate that a factor

issuing from the activated macrophages both enhances the activity of the myeloma cells and inhibits normal immunoglobulin production and T lymphocyte function.

Myeloma patients are susceptible to both viral infections and infections with “encapsulated” bacteria such as pneumococcus. However, in the face of neutropenia, the effects of high-dose chemotherapy, and with the added local effects of implanted catheters (e.g., Hickman and Groshon catheters or PICC lines), a large range of bacterial, fungal, and opportunistic infections can occur in myeloma patients undergoing therapy.

**In summary, key aspects of infections in myeloma patients are:**

- **Reduced immunity** because of myeloma.
- **Low white blood cell counts** because of myeloma build-up in bone marrow and/or the impact of treatment.

**Infection, or any question of infection, should not be ignored. Prompt review is required to assess the need for immediate antibiotic and/or antiviral therapy.** Many patients learn to have therapy on hand for any emergency.

### Types of myeloma

The type of monoclonal protein produced varies from patient to patient. The most common monoclonal protein is IgG and the least common is IgE. The accompanying Table shows the percentages of different types of myeloma. Each type is associated with slightly different patterns of disease. For example, IgA myeloma is more commonly associated with disease outside bone (extramedullary disease), whereas IgD myeloma is more commonly associated with plasma cell leukemia and renal damage.

### Clinical symptoms

About 70% of patients with myeloma present with pain of varying intensity, often in the lower back or ribs. Sudden, severe pain can be a sign of fracture or the collapse of a vertebral body. General malaise and vague complaints are frequent. Significant weight loss is rare.

Both neutropenia and hypogammaglobulinemia (immunoparesis) increase the likelihood of infections. Although pneumococcal pneumonia is the classic infection associated with myeloma at presentation, other bacteria, such as streptococci and staphylococci, are now frequently isolated. Haemophilus infection and herpes zoster infections also occur.

Hypercalcemia, historically found in 30% of patients at the time of diagnosis, causes tiredness, thirst, and nausea. Precipitation of calcium

**Table 3. Types of monoclonal protein (%)\***

	%	Totals
1. Serum		
IgG	52	75%
IgA	21	
IgD	2	
IgE	< 0.01	
2. Urine (Bence Jones or light chains only) types κ and λ		11%
3. Two or more monoclonal paraproteins	< 1	2%
Heavy chains (G or A) only	< 1	
No monoclonal paraprotein	1	
4. IgM (rarely myeloma, typically associated with Waldenström’s macroglobulemia)		12%
<b>Total</b>		<b>100%</b>

\* This includes different types of MGUS and myeloma as well as Waldenström’s macroglobulemia.  
Source: Data on 1,827 myeloma patients collected and analyzed by W Pruzanski and MA Ogryzlo, 1970.

salts can result in deterioration of kidney function. Yet, in recent years the incidence of hypercalcemia in newly diagnosed patients has dropped to 10%–15%, most likely because of earlier diagnosis. In Latin America and some parts of Asia where late diagnosis is common, hypercalcemia remains more common.

Hyperviscosity resulting from high levels of myeloma protein can cause problems such as bruising, nose bleeding, hazy vision, headaches, gastrointestinal bleeding, sleepiness, and a variety of ischemic neurological symptoms caused by reduced blood and oxygen supply to the nerve tissue. Hyperviscosity occurs in <10% of patients with myeloma and in about 50% of patients with Waldenström’s macroglobulinemia (all of whom have IgM paraprotein or M-component). Increased bleeding is often exacerbated by thrombocytopenia as well as by binding of monoclonal proteins to clotting factors and/or platelets.

Depending on the location of affected nerves, neurologic involvement can result in specific problems. Particularly common problems are spinal cord compression, meningitis, and carpal tunnel syndrome. Although the first two are the result of plasma cell tumor formation or infiltration, carpal tunnel syndrome in myeloma patients usually results from amyloid deposition (deposition of Bence Jones proteins in a special beta-pleated form).

Staging and prognostic factors

Prognosis in myeloma is determined by both the number and specific properties of myeloma cells in a given patient. These specific properties include the growth rate of myeloma cells, the production rate of monoclonal proteins, and the production or non-production of various cytokines and chemicals that damage or significantly impair other tissues, organs, or bodily functions. In 1975, the Durie-Salmon Staging System was developed, bringing together major clinical parameters in correlation with measured myeloma cell mass (the total number of myeloma cells in the body). In 2005, a new staging system was developed by the IMF-sponsored IMWG. Clinical and laboratory data were gathered on 10,750 previously untreated symptomatic myeloma patients from 17 institutions, including sites in North America, Europe, and Asia. Potential prognostic factors were evaluated using a variety of statistical techniques. Serum β2 microglobulin (Sβ2M), serum albumin, platelet count, serum creatinine, and age emerged as powerful predictors of survival and were then further analyzed.

A combination of Sβ2M and serum albumin provided the most powerful, simple, and reproducible three-stage classification. The ISS was further validated by demonstrating effectiveness in patients in North America,

Europe, and Asia; in patients younger and older than age 65 years; with standard therapy or auto transplant; and in comparison with the Durie-Salmon Staging System. In August 2015 the IMWG published the *Revised International Staging System (R-ISS) for multiple myeloma* in order to incorporate two further prognostic factors: genetic risk as assessed by FISH and level of LDH.

Myeloma can be classified based upon genetic risk using molecular fluorescence in situ hybridization (FISH) and cytogenetic abnormalities identified in bone marrow myeloma cells. Such classification can have important implications for treatment. Higher-risk disease is defined as the presence of any one of the following genetic mutations: t(4;14), t(14;16), t(14;20), or deletion of 17p by FISH. It is crucial to be aware that treatment selection is influenced by genetic risk. For example, the presence of t(4;14), which has been noted as a poor risk factor in the past, has largely been overcome with the use of Velcade (bortezomib) combination regimens. There is also a positive impact of lenalidomide-containing regimens in patients with t(4;14) in several Revlimid clinical trials. A report from the IFM group indicated that the presence of t(14;16) was also no longer a predictive

Table 4. Standard risk factors for multiple myeloma and the R-ISS

PROGNOSTIC FACTOR		CRITERIA
ISS Stage	I	Serum β2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
	II	Not ISS stage I or III
	III	Serum β2-microglobulin ≥ 5.5 mg/L
CA by iFISH	High Risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
	Standard Risk	No high-risk CA
LDH	Normal	Serum LDH < the upper limit of normal
	High	Serum LDH > the upper limit of normal
A new model for risk stratification for multiple myeloma		
R-ISS Stage	I	ISS stage I and standard-risk CA by iFISH and normal LDH
	II	Not R-ISS stage I or III
	III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; R-ISS, Revised International Staging System.



prognostic factor in their clinical trials, while IFM findings published in February 2015 indicate that in early relapse, Pomalyst is an effective treatment for those with deletion 17p. Improved and more effective risk classification systems are being developed and evaluated with the expectation that it will be possible to offer treatment selection based upon documented treatment outcomes with new combination approaches.

One such new risk classification system is microarray-based gene expression profiling (GEP), which has been used to assess risk in myeloma patients both at diagnosis and at relapse. Approximately 15% of newly diagnosed patients assessed with GEP in clinical trials have shown a high-risk GEP signature. Such patients have shorter durations of complete remission, event-free survival, and OS. Although GEP has the potential to further refine risk prognosis beyond standard cytogenetics (karyotyping) and FISH, its use is currently limited by the lack of a uniform platform across many centers in the world and by widespread unavailability.

Definition of clinical response

The IMWG uniform response criteria are recommended to classify response to treatment. Improvements in M-component must be associated with evidence of clinical improvement (such as reduced bone pain and/or improved red blood cell counts). It is important to keep in mind that a higher percent regression does not automatically confer longer survival. When there is residual disease, the characteristics of the remaining drug-resistant myeloma cells determine the outcome. These remaining myeloma cells may or may not have tendency for immediate regrowth. If there is no regrowth, this is called “plateau phase”: residual but stable disease. The fraction of resistant myeloma cells is primarily dependent upon the intrinsic molecular features of the individual myeloma and the pre-treatment tumor burden or stage. Responding patients go from a high-risk status to a lower-risk status until, ideally, no signs of myeloma are left, or they reach a stable plateau phase, but with measurable residual disease. The time required to reach the plateau phase is variable, ranging from three to six months (rapid response), to 12 to 18 months (slow response).

As treatment has improved, it has become more important to assess response to treatment as accurately as possible. Besides the depth of response, which is indicated by PR (≥ 50% improvement), VGPR (≥ 90%), or CR (100% reduction in monoclonal protein), one must now consider even deeper responses as well as duration of response. With the increasing efficacy of new combination therapies, it is now necessary to add the terms “minimal residual disease (MRD)” and “MRD-negative” to the response criteria, concepts that were previously unattainable and unmeasurable

in myeloma. Minimal disease levels are now not only possible to achieve, but are verifiable with next-generation DNA sequencing (NGS) and next-generation flow cytometry (NGF) performed on bone marrow samples. Both NGS and NGF are sensitive to 10<sup>-6</sup>, meaning that they can detect a single myeloma cell among a million sampled cells.

The FDA is in the process of reviewing data on NGF, the 8-color, 2-tube EuroFlow® test developed at the University of Salamanca, Spain. If approved, NGF MRD testing will become the new clinical trial endpoint – the standard means to measure depth of response in US-based myeloma clinical trials. In addition, another group of previously approved tests is demonstrating utility in detecting minimal residual disease. The heavy + light chain isotype (Hevylite) assays measure monoclonal and polyclonal intact immunoglobulins and the ratio between them. These tests have shown that at the deepest level of response, HLC ratios provide additional sensitivity over conventional assessments with serum and urine electrophoresis. The *International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma* was published in *Lancet* in 2016.

Table 5. IMWG criteria for response assessment including criteria for MRD

IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD (minimal residual disease) negativity in the marrow – NGF (next-generation flow), or NGS (next-generation sequencing), or both – and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10 <sup>5</sup> nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 <sup>5</sup> nucleated cells or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV (maximum standardized uptake value) or decrease to less than that of surrounding normal tissue

(Table 5 continues on next page)

**Table 5. IMWG criteria for response assessment including criteria for MRD**  
(continued from previous page)

<b>Standard IMWG response criteria</b>
<b>Stringent complete response</b>
Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry ( $\kappa/\lambda$ ratio $\leq 4:1$ or $\geq 1:2$ for $\kappa$ and $\lambda$ patients, respectively, after counting $\geq 100$ plasma cells)
<b>Complete response</b>
Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $< 5\%$ plasma cells in bone marrow aspirates
<b>Very good partial response</b>
Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level $< 100$ mg per 24 h
<b>Partial response</b>
<ul style="list-style-type: none"> <li><math>\geq 50\%</math> reduction of serum M-protein plus reduction in 24 h urinary M-protein by <math>\geq 90\%</math> or to <math>&lt; 200</math> mg per 24 h;</li> <li>If the serum and urine M-protein are unmeasurable, a <math>\geq 50\%</math> decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria;</li> <li>If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, <math>\geq 50\%</math> reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was <math>\geq 30\%</math>;</li> <li>In addition to these criteria, if present at baseline, a <math>\geq 50\%</math> reduction in the SPD (sum of the products of the maximal perpendicular diameters of measured lesions) of soft tissue plasmacytomas is also required</li> </ul>
<b>Minimal response</b>
<ul style="list-style-type: none"> <li><math>\geq 25\%</math> but <math>\leq 49\%</math> reduction of serum M-protein and reduction in 24-h urine M-protein by <math>50\% - 89\%</math>;</li> <li>In addition to the above listed criteria, if present at baseline, a <math>\geq 50\%</math> reduction in the size (SPD) of soft tissue plasmacytomas is also required</li> </ul>
<b>Stable disease</b>
Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease

(Table 5 continues on next page)

**Table 5. IMWG criteria for response assessment including criteria for MRD**  
(continued from previous page)

<b>Standard IMWG response criteria (continued)</b>
<b>Progressive disease</b>
<p>Increase of 25% from lowest confirmed response value in any one or more of the following criteria:</p> <ul style="list-style-type: none"> <li>Serum M-protein (absolute increase must be <math>\geq 0.5</math> g/dL);</li> <li>Serum M-protein increase <math>\geq 1</math> g/dL, if the lowest M component was <math>\geq 5</math> g/dL;</li> <li>Urine M-protein (absolute increase must be <math>\geq 200</math> mg/24 h);</li> <li>In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be <math>&gt; 10</math> mg/dL);</li> <li>In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be <math>\geq 10\%</math>);</li> <li>Appearance of a new lesion(s), <math>\geq 50\%</math> increase from nadir in SPD of <math>&gt; 1</math> lesion, or <math>\geq 50\%</math> increase in the longest diameter of a previous lesion <math>&gt; 1</math> cm in short axis;</li> <li><math>\geq 50\%</math> increase in circulating plasma cells (minimum of 200 cells per <math>\mu\text{L}</math>) if this is the only measure of disease</li> </ul>
<b>Clinical Relapse</b>
<p>Clinical relapse requires one or more of the following criteria:</p> <ul style="list-style-type: none"> <li>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;</li> <li>Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);</li> <li>Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and <math>\geq 1</math> cm) increase as measured serially by the SPD of the measurable lesion;</li> <li>Hypercalcemia (<math>&gt; 11</math> mg/dL);</li> <li>Decrease in hemoglobin of <math>\geq 2</math> g/dL not related to therapy or other non-myeloma-related conditions;</li> <li>Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;</li> <li>Hyperviscosity related to serum paraprotein</li> </ul>
<b>Relapse from complete response (to be used only if the end point is disease-free survival)</b>
<p>Any one or more of the following criteria:</p> <ul style="list-style-type: none"> <li>Reappearance of serum or urine M-protein by immunofixation or electrophoresis;</li> <li>Development of <math>\geq 5\%</math> plasma cells in the bone marrow;</li> <li>Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia see above)</li> </ul>
<b>Relapse from MRD negative (to be used only if the end point is disease-free survival)</b>
<p>Any one or more of the following criteria:</p> <ul style="list-style-type: none"> <li>Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);</li> <li>Reappearance of serum or urine M-protein by immunofixation or electrophoresis;</li> <li>Development of <math>\geq 5\%</math> clonal plasma cells in the bone marrow;</li> <li>Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)</li> </ul>

Important terms in assessing response are:

- TTP – Time To Progression: the time from start of treatment until relapse occurs.
- PFS – Progression-Free Survival: the length of survival during which the patient is still in remission\*.
- PFS1 – As defined by A Palumbo, the time from the start of therapy to the occurrence of first relapse.
- PFS2 – The time from start of therapy to the occurrence of second relapse, incorporating the duration of both first and second remissions.

*\*Remission is generally considered to be at least a partial response (PR,  $\geq 50\%$  improvement) which lasts for at least 6 months.*

## Treatment

### Exclude MGUS or asymptomatic myeloma

The first and most important decision when dealing with myeloma is to determine if treatment is required. Patients with MGUS and standard- or low-risk asymptomatic or smoldering myeloma should be closely observed rather than treated. There are currently ongoing clinical trials using various therapeutic regimens to treat high-risk and standard-risk smoldering myeloma and several clinical trials that are attempting to determine if it is possible to enhance the immune regulation of early myeloma or reduce the likelihood of disease activation.

Of note are two completed studies: The Spanish group's PETHEMA clinical trial for high-risk SMM in which patients were either observed or treated with lenalidomide and dexamethasone, and the NCI study of carfilzomib, lenalidomide, and dexamethasone for patients with high-risk SMM. In the Spanish clinical trial, disease progression was delayed and OS at a median of six years was significantly improved among patients who were treated with lenalidomide and low-dose dexamethasone as compared to those who were observed. In the NCI pilot study, which was presented at ASH 2014, the combination of carfilzomib, lenalidomide, and dexamethasone in the 12 enrolled patients resulted in a 100% complete response rate over the course of the study. Moreover, 11 of the 12 patients who responded have maintained their MRD negativity. They are being followed to assess the duration of their MRD-negative status.

As part of its Black Swan Research Initiative, the IMF is supporting two clinical trials dubbed "Cure Trials" to treat patients with high-risk smoldering myeloma. These studies are designed to treat asymptomatic disease early and aggressively in an attempt to reach sustained MRD

negativity and cure before clonal evolution and end-organ damage occur. The fully-accrued CESAR clinical trial, using carfilzomib + lenalidomide + dexamethasone (KRd) before and after ASCT followed by 24 months of Rd, is being conducted in Spain. The US clinical trial, ASCENT, using KRd plus daratumumab for 12 cycles followed by 2 years of maintenance with carfilzomib + daratumumab, will begin accruing patients in 2018.

## New diagnostic criteria

The IMWG published *Updated Criteria for the Diagnosis of Myeloma* (SV Rajkumar et al., *Lancet*, 2014) in order to accurately identify "the subset of patients with smoldering multiple myeloma and biological malignancy who are at imminent risk of developing CRAB features." The validated criteria for "ultra-high-risk" SMM, now defined as active myeloma, are:

- At least 60% plasmacellularity of bone marrow.
- A ratio of involved to uninvolved free light chains of at least 100.
- Two or more focal lesions > 5 mm on MRI.

**Table 6. Myeloma treatment options**

1. Induction therapy
2. High-dose chemotherapy with hematopoietic stem cell transplant
3. Conservative use of radiation to preserve bone marrow
4. Maintenance therapy
5. Supportive care:
<ul style="list-style-type: none"> <li>• Pain medication</li> <li>• Anti-viral therapy</li> <li>• Emergency care (e.g., dialysis, plasmapheresis, surgery, radiation)</li> <li>• Bisphosphonates</li> <li>• Brace/corset</li> <li>• Growth factors</li> <li>• Exercise</li> <li>• Antibiotics</li> <li>• Kypholasty/vertebroplasty</li> </ul>
6. Management of drug-resistant or refractory disease
7. Novel and experimental therapies:
<ul style="list-style-type: none"> <li>• Immunomodulatory drugs Thalomid® (thalidomide), Revlimid® (lenalidomide), Pomalyst® (pomalidomide)</li> <li>• Approved injectable proteasome inhibitors Velcade® (bortezomib) and Kyprolis® (carfilzomib), and oral proteasome inhibitor Ninlaro® (ixazomib); oral proteasome inhibitors oprozomib and marizomib in clinical trials</li> <li>• Histone deacetylase (HDAC) inhibitor Farydak® (panobinostat); HDAC inhibitor ACY-241 in clinical trials</li> <li>• Immunotherapies pembrolizumab, pidilizumab, lambrolizumab, CART cells in clinical trials</li> <li>• Monoclonal antibodies Darzalex® (daratumumab) and Empliciti® (elotuzumab); isatuximab (SAR650984) and siltuximab in clinical trials</li> <li>• Pan-tumor suppressor gene promoter selinexor in clinical trials</li> </ul>

Because these criteria have individually been proven to carry an 80% or greater risk of progression to active disease within 18 months to two years, any one of them is considered a “myeloma-defining event.” *Thus, asymptomatic patients with any of these criteria should be considered to have early active myeloma and should be treated, not merely observed.* This is a major paradigm shift in myeloma, as previous wisdom held that all asymptomatic patients be observed until one or more of the CRAB criteria were manifest. Because there are now treatment tools available to prevent disease progression and potentially cure myeloma before it causes end-organ damage, it is now imperative to intervene in early active disease.

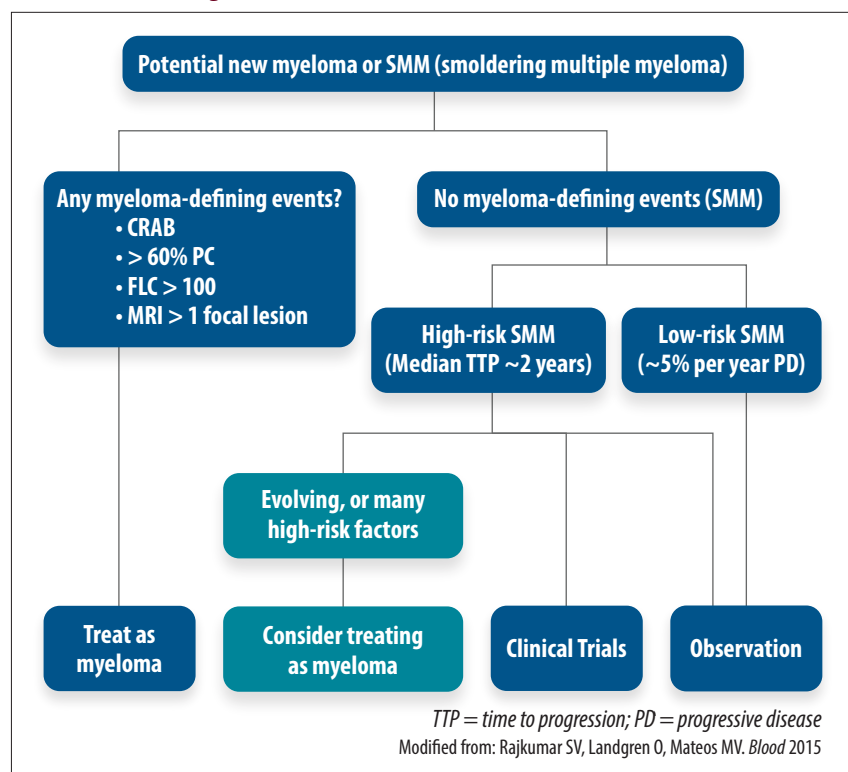
Specific anti-myeloma treatment is recommended when active myeloma has developed, as reflected by an increasing M-component, emerging or imminent clinical problems, or “CRAB” features. Problems sufficient to require treatment include bone destruction (lytic lesions and/or osteoporosis), renal insufficiency, progressive reduction in blood counts (e.g., anemia, neutropenia), elevated blood calcium, nerve damage, or other significant organ or tissue damage caused by myeloma or

myeloma protein. These indications for the need to start treatment can be summarized as CRAB features: **C**alcium elevation, **R**enal problems, **A**nemia, or **B**one issues. The overall goals of treatment are to address specific problems and to achieve general control of the disease. A summary of types of treatments is provided in the accompanying Table, and an algorithm presented by Mayo Clinic’s Dr. Vincent Rajkumar at the IMF’s 2017 ASH satellite symposium, “Getting Clear Answers to Complex Treatment Challenges in Multiple Myeloma” shows when treatment should be initiated in potential new myeloma or smoldering myeloma.

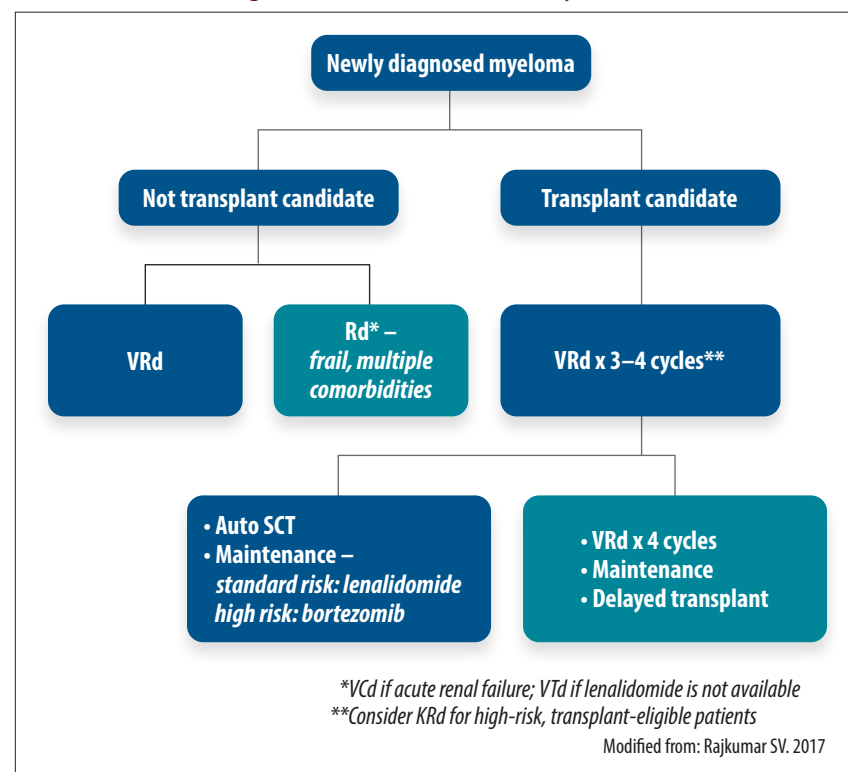
## Treatment overview

Please see the History section for an overview of the evolution of presently used treatments. Since melphalan was first introduced in 1962, various combination chemotherapy regimens have been used and attempts have been made to improve outcomes using high-dose chemotherapy regimens with bone marrow transplant (BMT) or peripheral blood stem cell transplant (PBSCT). In the standard type of BMT or PBSCT, the

**Figure 5. When should treatment be started?**



**Figure 6. Initial treatment of myeloma**





“transplant” is a “rescue” with normal bone marrow stem cells after the stem cells in the body have been destroyed by high-dose chemotherapy (usually melphalan).

In the 1980s and 1990s, high-dose melphalan with stem cell rescue was one of the few techniques available to reduce myeloma tumor burden and achieve better outcomes. With the introduction of thalidomide for myeloma treatment in 1997, the options for treatment expanded. Complete responses could be achieved with a simple oral agent. Additional novel agents followed soon after: first bortezomib in 2003, then lenalidomide in 2005, carfilzomib in 2012, pomalidomide (2013), panobinostat (2015), and in rapid succession in November 2015, daratumumab, ixazomib, and elotuzumab. The addition of these new agents to the myeloma armamentarium has left practitioners somewhat at a loss as to best combinations and sequencing. What has become increasingly clear, however, is that no single therapy is likely to be effective for every myeloma patient, nor is any single agent likely to achieve a cure on its own. Rather, the combination approach that attacks myeloma cells with multiple drugs through multiple pathways has thus far demonstrated superior efficacy. This concept was amply demonstrated by the long-awaited results of the SWOG S0777 multi-center clinical trial, which were presented at ASH 2015 and published in *The Lancet* in January 2017. This clinical trial compared Velcade + Revlimid + dexamethasone (VRd) to Revlimid + dexamethasone (Rd) in newly diagnosed patients who were not candidates for transplant. The data demonstrated that PFS and OS were a year longer with VRd than with Rd. These data firmly establish the superiority of triplet frontline therapy and confirm the efficacy of the combination of a proteasome inhibitor and an immunomodulatory drug.

There is no simple answer to the question of “the best” treatment options available today. Fortunately, there are numerous regimens that can produce very deep and durable responses (remissions lasting ≥ 2 years) and improved OS. The best choice for each patient

**Table 7. Frontline treatment options for patients not eligible for transplant**

<b>Frail Patients: Two-drug regimen</b>
<ul style="list-style-type: none"><li>• Revlimid + low-dose dexamethasone (Rd)</li><li>• Velcade + low-dose dexamethasone (Vd)</li></ul>
<b>Fit Patients: Three-drug regimen</b>
<ul style="list-style-type: none"><li>• Velcade + Revlimid + dexamethasone (VRD or RVD)</li><li>• Reduced-dose VRD (VRD-lite)</li><li>• Velcade + Cytoxan + dexamethasone (VCD or CyBorD)</li><li>• Velcade + thalidomide + dexamethasone (VTD)</li><li>• Cytoxan + thalidomide + dexamethasone (CTD)</li><li>• Velcade + melphalan + prednisone (VMP)</li><li>• VMP ± Rd (sequential or alternating)</li><li>• Other</li></ul>

depends upon individual factors such as age, stage, genetic features, kidney status, comorbidities, cost, and of course, personal preference. Myeloma patients must be aware of the need for careful discussions with their physicians about treatment choices.

**Options for patients who are not candidates for stem cell transplant**

The approach to frontline treatment has changed substantially with the introduction of novel agents thalidomide, bortezomib, lenalidomide, and carfilzomib. Selection of frontline therapy should be tailored to the patient’s fitness status and to the presence or absence of kidney disease, peripheral neuropathy, and high-risk genetic mutations. At the present time, almost all patients in the US receive induction therapy that includes at least one novel agent. Most patients in the US receive VRd combination therapy. The thalidomide + dexamethasone combination is presently less frequently used because of the availability of next-generation IMiDs and their relatively favorable side effects profile in comparison to thalidomide-related adverse events that include thrombosis, fatigue, cytopenia, and peripheral neuropathy.

Current NCCN Guidelines for treatment of newly diagnosed patients who are not candidates for high-dose therapy with stem cell transplant list VRd as the preferred category 1 treatment option. Other preferred options are Rd and VCd (bortezomib, cyclophosphamide, and dexamethasone).

The 2013 publication of the IFM’s three-arm FIRST clinical trial comparing continuous Revlimid + dexamethasone therapy to fixed-dose Revlimid + dexamethasone and to MPT not only led to the 2015 FDA and EMA approvals of frontline Revlimid + dexamethasone, but demonstrated the superiority of continuous therapy with Revlimid over fixed-dose Revlimid or MPT.

The *International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem cell transplantation* (A Palumbo et al. *JCO* January 13, 2014) recommends that older, sometimes frailer, patients be treated according to their fitness level. *Geriatric assessment predicts survival and toxicities in elderly myeloma: an International Myeloma Working Group report* (A Palumbo et al. *Blood* January 27, 2015) is a geriatric assessment tool developed to assess comorbidities, cognitive abilities, and physical status. The tool predicts mortality and the risk of toxicity in elderly myeloma patients, which helps to tailor therapy appropriately. The guidelines recommend that while it is usually preferable to treat the elderly frail patient with a two-drug regimen (Velcade + dexamethasone or Revlimid +

dexamethasone), fit, newly diagnosed patients who are not eligible for transplant should be treated with three-drug regimens such as RVD or its variant, reduced-dose “VRD lite”; CyBorD (cyclophosphamide + bortezomib + dexamethasone); and more commonly outside the US, CTD (cyclophosphamide + thalidomide + dexamethasone) or VMP (Velcade + melphalan + prednisone).

**Table 8. Induction therapy options for transplant-eligible patients**

<b>Velcade-based triple therapy</b>
• Velcade + Cytoxan + dexamethasone (VCD or CyBorD)
• Velcade + Revlimid + dexamethasone (VRD or RVD)
• Velcade + thalidomide + dexamethasone (VTD)
• Velcade + Adriamycin + dexamethasone (PAD)
<b>Kyprolis-based triple therapy</b>
• Kyprolis + Cytoxan + dexamethasone (KCD)
• Kyprolis + Revlimid + dexamethasone (KRD)
• Kyprolis + thalidomide + dexamethasone (KTD)
• Other

## If stem cell harvest is planned

Patient age of > 70 years is not an absolute deterrent to stem cell transplant. A Hackensack University Medical Center study presented at the ASH meeting in December 2017, followed autologous transplant patients aged 75 to 81 years of age. The researchers concluded that there was no difference in overall survival at five years of follow-up among this group of elderly patients compared to patients younger than age 75. Whether or not autologous transplant is an appropriate option must be discussed with each patient on an individual basis, taking into account fitness, genetic risk factors, family and work considerations, and personal preference.

The approach to induction therapy prior to stem cell harvest and high-dose therapy with stem cell rescue has evolved considerably over the last two decades. The former standard induction regimen has now been supplanted by more effective combination regimens with less toxicity.

Current NCCN guidelines for newly diagnosed patients eligible for stem cell transplantation indicate that the preferred regimen is VRd. Other recommended therapies include:

- bortezomib, doxorubicin, dexamethasone (PAD)
- carfilzomib, lenalidomide, dexamethasone (KRD)
- ixazomib, lenalidomide, dexamethasone (IRd)

## Caveats for various induction options

Three-drug regimens can produce rapid responses and high response rates.

- Regimens containing lenalidomide and dexamethasone carry an increased risk of blood clots (deep vein thrombosis, DVT) and

**Table 9. Most commonly used chemotherapy drugs**

DRUG NAME	OTHER TREATMENT NAME	COMMENTS
<b>Traditional Agents</b>		
melphalan* (M)**	Alkeran® (by mouth or IV)	Best single agent for treatment
cyclophosphamide* (C or CY)**	Cytosan® (by mouth or IV)	Similar efficacy to M but with more GI and GU toxicity and less bone marrow stem cell injury
prednisone (P)**	Prednisolone® (similar) (usually by mouth)	Directly active, works well with M, C, and B. Does not produce suppression of bone marrow
dexamethasone (D)**	Decadron® (by mouth or IV)	Similar to prednisone but more potent; more severe side effects
<b>Novel Agents</b>		
Pegylated, liposomal doxorubicin*	Doxil® (IV)	In combination, promising activity, less toxicity than A
bortezomib (B, V, or P)**	Velcade® (IV)	Directly active, used alone or in combination
daratumumab	Darzalex®	Approved for use as a single agent in patients who have had at least 3 lines of therapy
elotuzumab	Empliciti®	Approved for use in combination with lenalidomide + dexamethasone in patients who have had 1–3 prior lines of therapy
ixazomib	Ninlaro®	Approved for use in combination with lenalidomide + dexamethasone in patients who have had 1 prior therapy
thalidomide (T)**	Thalomid® (by mouth)	Directly active, approved for use in combination with dexamethasone, used in other combinations
lenalidomide (R or L)**	Revlimid® (by mouth)	Directly active, approved for use in combination with dexamethasone, used in other combinations
carfilzomib	Kyprolis® (IV)	Directly active, used alone or in combination
pomalidomide	Pomalyst® (by mouth)	Directly active, used alone or in combination
panobinostat	Farydak® (by mouth)	Approved for use in combination with bortezomib and dexamethasone

\*Alkylating agents \*\*Common abbreviation

require prophylactic aspirin or another anticoagulant treatment. Patients receiving induction therapy prior to ASCT with a lenalidomide-containing regimen should have their stem cells mobilized and harvested after no more than four cycles of therapy.

- Neuropathy is a concern with the thalidomide- and Velcade-containing regimens. Supplements such as the amino acids L-carnitine and L-glutamine and vitamins B6 and B12 may offer some neuroprotection. A new mRNA test is in development that would identify myeloma patients at risk for bortezomib-induced peripheral neuropathy, thus guiding treatment selection ahead of time.
- The incidence of peripheral neuropathy has been demonstrated to be significantly less with subcutaneous Velcade than with IV administration.
- The proteasome inhibitors and the monoclonal antibody daratumumab increase susceptibility to herpes zoster infection (shingles). Patients taking Velcade (bortezomib), Ninlaro (ixazomib), and Darzalex (daratumumab) should be given prophylactic antiviral therapy; prophylactic antiviral therapy should be considered for patients taking carfilzomib who have a prior history of herpes zoster infection.

It is a challenge to select the best treatment for each patient. One must consider the early risks of treatment, DVT and neuropathy risks, convenience, and costs. Presence of genetic high-risk features and/or renal compromise may sway the choice toward Velcade combinations. Open dialogue to discuss the pros and cons is crucial.

## Transplantation

### High-dose therapy (HDT) with autologous stem cell transplantation (ASCT)

- HDT with ASCT has been shown to improve both response rates and survival in patients with myeloma. However, this approach is not curative. With the introduction of novel combination therapies in addition to ASCT, some investigators are introducing the notion that a subgroup of patients (“good risk”) may have extended survival and may achieve “functional cure” (defined as complete remission for  $\geq 4$  years).
- Complete remission rates with HDT as a planned part of frontline therapy can now be  $\geq 90\%$  with new pre- and post-transplant strategies, with PFS rates extending to four years.

The final analysis of the pivotal IFM 2009 phase III randomized clinical trial of RVD with or without upfront ASCT was published in 2017 in the *New England Journal of Medicine*. In this clinical trial, 700 patients received standard induction with RVD for three cycles, followed by stem cell collection. Then, the patients were randomized to upfront ASCT followed by consolidation with two additional cycles of RVD versus eight cycles of RVD. Following completion of initial treatment, all patients received maintenance lenalidomide for one year. Median PFS (50 versus 36 months), rate of complete response (59% versus 48%), and absence of minimal residual disease (79% versus 65%) were improved with upfront transplant, although overall survival at 4 years did not differ significantly between the transplantation group and the RVD-alone group. PFS and MRD-negativity results from this clinical trial have established upfront transplant as the standard of care even in the context of novel drugs.

### Morbidity and mortality of autologous transplant

With current growth factor, antibiotic, and other supportive care, the procedure-related mortality with HDT is very low:  $< 5\%$ . The majority of centers use intravenous high-dose melphalan alone at a dose of 200 mg/m<sup>2</sup> as the preparative regimen.

### Current Recommendations

- **HDT with autologous stem cell support should be recommended as part of the frontline therapy for eligible newly diagnosed patients with symptomatic myeloma.**
- The standard conditioning regimen is melphalan 200 mg/m<sup>2</sup>. Total body irradiation is not recommended.
- Stem cell purging is not recommended because of added expense without additional clinical benefit.
- Peripheral blood stem cells are recommended over bone marrow because of ease of collection and more rapid engraftment.
- The pre-transplant regimens are discussed above.

### Role of auto transplantation at time of first relapse

Part of the decision process for autotransplant involves understanding the impact of waiting, with a view to transplant at relapse. Each patient and his or her physician must evaluate the relative risks and benefits of proceeding with, delaying, or foregoing transplant. Quality of life becomes an important consideration. If transplant is not performed as a planned primary strategy, then typically additional therapy, including maintenance, is required, with corresponding toxicity and side effects. Deferring the

disruptive impact of the transplant – which may be better for some patients – must be balanced against the risk of a shorter remission and the need for further therapy.

### Harvesting and storing stem cells for later use

There is a strong reluctance in many cancer centers to harvest stem cells without a clear plan for use, typically immediate use. This reluctance arises from protocol priorities, cost/utilization constraints for harvesting and storage, as well as numerous other factors. Current guidelines recommend harvesting enough stem cells for two transplants. If possible, we recommend that patients have their stem cells harvested, even though they may not be enthusiastic about immediate high-dose therapy.

#### Current Recommendations

- Harvesting with storage for future use with review on a case-by-case basis.
- There is medical and scientific rationale for saving stem cells for later use.
- Delayed transplant is a viable treatment option.
- A second transplant at relapse is a viable option, especially if a remission of >2 years has occurred following a first transplant. (See discussion of “double” transplantation.)

### The role of double or tandem transplantation

- At present, the added benefit of double or tandem transplantation versus a single autologous transplant is unclear.
- The results with planned primary tandem transplant (Total Therapy 1, 2, 3, 4, and 5 at the University of Arkansas) have been good. The median overall survival has been 68 months, with some sub-groups having even longer survival. Total Therapy 3, which incorporates the use of Velcade, appears to offer earlier response and increased response rates, although patients with high-risk factors, including older age, higher LDH, abnormal cytogenetics, or advanced disease, are not as likely to achieve extended benefit.
- Comparative studies, including the French randomized studies, have shown benefit predominantly for a subgroup of patients (those who are not in VGPR or CR).
- Data from the StaMINA clinical trial, the largest US transplant clinical trial ever conducted, were presented at ASH 2016. StaMINA, a three-arm study, compared single auto transplant, tandem transplant, and auto transplant followed by four cycles of RVD consolidation. Patients in all three arms received maintenance

therapy with Revlimid until disease progression. Trial data revealed no statistical difference in PFS or OS among the patients in the three arms at 38 months of study follow-up.

#### Current Recommendations

- At the present time, planned tandem transplant continues to be a clinical trial option and should be carried out at centers specialized in this approach. A planned second transplant can be considered in patients achieving < VGPR with a first auto transplant.
- A second transplant in a patient who has responded well with a first transplant and relapsed after > 2 years is a helpful and viable option.
- Saving and storing enough stem cells for a second or additional transplant, if appropriate, is strongly recommended.

### The role of allogeneic transplantation

- Despite medical improvements over the past two decades, full allogeneic transplant, even with a perfectly matched sibling donor, is a high-risk procedure in the management of myeloma. The initial treatment-related morbidity and mortality is high. Even at centers with the greatest experience, and in the best risk settings, initial mortality is at least 15% to 20%. In other centers, 20% to 30% or higher mortality is frequently reported. The pulmonary complications are usually the most critical for myeloma patients.
- The potential advantage of allogeneic transplantation – an early foray into “immunotherapy” – is the graft-versus-myeloma effect. But, despite this immunologic benefit, long-term cure is rare, and side effects can be debilitating, if not lethal. Relapse continues at a rate of approximately 7% per year with long-term follow-up.
- The graft-versus-myeloma effect can be enhanced by using donor lymphocyte infusions and has been clinically beneficial in some cases.
- Long-term follow-up data published by G Ghartan et al. in 2013 demonstrated that “long-term outcome in patients with myeloma was better with auto/reduced-intensity conditioning (RIC) allo as compared with auto only, and the auto/RIC allo approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation. Follow-up longer than five years is necessary for correct interpretation of the value of auto/RICallo in multiple myeloma.”

#### Current Recommendations

- Conventional full-match allogeneic transplantation is rarely recommended as a primary strategy because the risks are too high.



- “Mini” (or RIC, reduced-intensity conditioning) allogeneic transplantation is only recommended in a clinical trial setting. There has been increasing interest in the upfront use of allogeneic transplant for high-risk patients.
- Identical twin or “syngeneic” transplantation is a rare option, which is a safe procedure with good outcome and is recommended as a consideration when an identical twin is available.

**Table 10. High-Dose Therapy (HDT)**

TRANSPLANT TYPE	ADVANTAGES	DISADVANTAGES
<b>Single Autologous</b>		
<ul style="list-style-type: none"> <li>• 50% excellent remissions</li> <li>• At least as good as standard therapy regarding overall survival and probably better for patients with high S<math>\beta</math>2M</li> <li>• Basis for strategies to produce true remission or long-term cure</li> <li>• New preparative regimens may produce true complete remission</li> </ul>	<ul style="list-style-type: none"> <li>• Relapse pattern similar to standard chemotherapy</li> <li>• More toxic and expensive</li> <li>• Patients who decisively benefit from transplant not clearly identified</li> <li>• Maintenance therapy may still be required/recommended</li> </ul>	
<b>Double Autologous</b>		
<ul style="list-style-type: none"> <li>• 2002 update of French data indicates survival benefit for subset of patients not in CR or VGPR</li> <li>• Excellent results with tandem transplant (<i>see text</i>)</li> </ul>	<ul style="list-style-type: none"> <li>• Role of double versus single still unclear</li> <li>• Much more toxic and expensive versus single</li> <li>• No survival benefit if in CR or VGPR after first transplant</li> </ul>	
<b>Traditional Allogeneic</b>		
<ul style="list-style-type: none"> <li>• No risk of contamination of marrow/stem cells with myeloma</li> <li>• Possible graft-versus-myeloma effect to prolong remission</li> </ul>	<ul style="list-style-type: none"> <li>• Even for HLA identical siblings, significant risk of early complications and even death</li> <li>• Risk of complications unpredictable</li> <li>• Restricted to age &lt; 55</li> <li>• More toxic and expensive versus autologous</li> </ul>	
<b>Reduced-intensity conditioning (RIC) allogeneic transplant or “Mini-Allo”</b>		
<ul style="list-style-type: none"> <li>• Less toxic form of allo</li> <li>• Preparative chemotherapy usually well tolerated</li> <li>• Results in anti-myeloma immune graft</li> </ul>	<ul style="list-style-type: none"> <li>• Still produces graft-versus-host disease</li> <li>• Full benefits still unclear</li> <li>• Risk of initial mortality approximately 17%</li> <li>• Not recommended for myeloma patients outside the context of a clinical trial</li> </ul>	
<b>Identical Twin</b>		
<ul style="list-style-type: none"> <li>• No risk of myeloma contamination in transplanted cells</li> <li>• Much less risky than allogeneic transplant</li> </ul>	<ul style="list-style-type: none"> <li>• No graft-versus-myeloma effect</li> <li>• Need identical twin &lt; 55</li> </ul>	

## Radiation

### Radiation therapy is an important modality of treatment

For patients with severe local problems such as bone destruction, severe pain, and/or pressure on nerves or the spinal cord, local radiation can be dramatically effective. The major disadvantage, however, is that radiation therapy permanently damages normal bone marrow stem cells in the area of treatment. Wide-field radiation encompassing large amounts of normal bone marrow should be avoided. A general strategy is to rely on systemic chemotherapy to achieve overall disease control, limiting the use of local radiation therapy to areas with particular problems.

## Maintenance therapy

**Immunomodulatory drugs** – In 2012, three randomized placebo-controlled clinical trials reported a significant prolongation of progression-free survival with Revlimid as maintenance therapy for myeloma. Two of these clinical trials looked at post-transplant maintenance, and the third clinical trial evaluated Revlimid as maintenance following standard melphalan-based therapy. The US CALGB study’s (P McCarthy et al.) initial results demonstrated that lenalidomide at a dose of 10 mg per day for 21 out of 28 days doubles time to progression compared with placebo when given to patients with stable disease or better after high-dose melphalan and ASCT. Follow-up data from that clinical trial demonstrated that lenalidomide maintenance also increases overall survival. An international meta-analysis of all three clinical trials presented by Dr. Philip McCarthy at the American Society of Clinical Oncology (ASCO) meeting in June 2016 demonstrated that continuous lenalidomide following autologous stem cell transplantation improved overall survival in these patients. The benefit in overall survival was consistent across subgroups. Based on these data, the FDA approved Revlimid for use as maintenance therapy after autologous stem cell transplant in newly diagnosed myeloma patients in February 2017. Two ASH presentations in 2017 – one from the UK, the other from Spain – reinforced the PFS, OS, and MRD-negativity benefits of Revlimid maintenance therapy, regardless of patients’ cytogenetic status.

Balanced against the favorable data on maintenance with lenalidomide is the low but increased risk of a second malignancy. A follow-up study by A Palumbo of the Italian group determined that lenalidomide alone does not increase the risk of second malignancy, but that the combination of melphalan and lenalidomide, two agents that can take a toll on the bone marrow, does. The final analysis of survival outcomes in the phase III FIRST clinical trial of continuous therapy with Rd in newly diagnosed, non-transplant eligible patients was published in *Blood* in November 2017.

That seminal clinical trial not only demonstrated the survival benefit of continuous therapy with Revlimid, but demonstrated that, absent stem cell transplant, there was no increased risk for secondary malignancies.

**Thalidomide** – A 2012 meta-analysis of patients receiving thalidomide maintenance therapy demonstrated that patients had marginally better overall survival. Thalidomide maintenance, however, increases the risk of venous thrombosis and peripheral neuropathy.

**Velcade (bortezomib)** – The Dutch-Belgian/German randomized phase III clinical trial known as HOVON-65/GMMG-HD4, comparing PAD plus bortezomib maintenance to VAD plus thalidomide maintenance, was published in August 2012. Not only did bortezomib result in improved PFS and OS, but its use as maintenance therapy administered on an every-other-week schedule was well tolerated and resulted in additional responses, especially in patients with renal failure, 13q deletion, and 17p deletion. While retrospective studies of bortezomib maintenance have been published, no other prospective, randomized clinical trial has been performed to date. Myeloma experts have, however, long used and recommended bortezomib or carfilzomib maintenance therapy for patients with the t(4;14), del 17p, t(14;16), and t(14;20) chromosomal abnormalities – the so-called “high-risk” genetic mutations (see Mayo Clinic’s MSMArt guidelines at <https://www.msma rt.org/mm-treatment-guidelines.html>).

A retrospective study from Duke University published in *Bone Marrow Transplantation* in April 2018, compares post-autologous transplant maintenance therapy with bortezomib versus Revlimid. While the study has its limitations, it does raise an important issue that remains to be addressed. The study found that neither maintenance therapy choice nor cytogenetic risk impacted PFS or OS among the 156 patients whose records were reviewed. However, the study did find that the risk of a second primary malignancy was 5.4% among patients on Revlimid maintenance versus 3% for those on bortezomib. The Duke investigators conclude that their data should be “validated in a larger, prospective cohort to determine if maintenance choice should be guided by side effect profile and patient anticipated tolerance rather than by disease biology alone.”

**Kyprolis (carfilzomib)** – A number of ongoing clinical trials in the US and Europe are evaluating the role of carfilzomib both as post-ASCT maintenance therapy and as continuous therapy in non-transplant clinical trials. Given that it does not cause peripheral neuropathy and that it is an irreversible inhibitor of the proteasome, carfilzomib given on a modified schedule may be safe and effective in the maintenance setting.

**Ninlaro (ixazomib)** – An integrated analysis of data from 121 newly diagnosed patients in four early-phase maintenance or continuous therapy studies was presented at ASH 2017. The data demonstrated that patients who continued on single-agent ixazomib following a ixazomib-based induction regimen had deepening of responses and good long-term outcomes, with median PFS of 21.4 months. Clinical trials with ixazomib in the maintenance setting are ongoing.

Supportive care

A full range of supportive care is crucial for the management of myeloma. When first diagnosed, a number of emergency procedures may be required, including dialysis, plasmapheresis, surgery, and radiation to reduce pressure on a nerve, the spinal cord, or other crucial organ. The management of pain is essential for the initial care of patients with myeloma. This can be difficult until initial disease control is achieved. There is no reason for patients with myeloma to have major ongoing

Table 11. Tests required to monitor therapy responses

Blood Tests		
• Routine blood counts	• Myeloma protein measurements (serum protein electrophoresis plus quantitative immunoglobulins)	
• Chemistry panel	• Serum free light chain assays (Freelite®)	
• Liver function tests	• Heavy/light chain assay (Hevylite®)	
• Serum β2 microglobulin	• Peripheral blood labeling index (LI)	
• C-reactive protein		
• Serum erythropoietin level		
Urine		
• Routine urinalysis		
• 24-hour urine for measurement of total protein, electrophoresis, and immunoelectrophoresis		
• 24-hour urine for creatinine clearance if serum creatinine elevated		
Bone Evaluation		
• Skeletal survey by X-ray	• Whole body FDG/PET scan if disease status unclear	
• MRI/CT scan for special problems	• Bone density measurement (DEXA scan) as baseline and to assess benefit of bisphosphonates	
Bone Marrow		
• Aspiration and biopsy for diagnosis and periodic monitoring		
• Special testing to assess prognosis looking for multiple potential karyotypic and FISH abnormalities (number of chromosomes, translocations, deletions – e.g., FISH 13q-, t[4;14], 1q21, etc.)		
Other Testing (special circumstances)		
• Amyloidosis	• Neuropathy	• Renal or infectious complications

pain with the range of new drugs and strategies available. There can be reluctance on the part of the patient and/or the physician to implement full pain control procedures because of concerns about addiction. Control of pain should always be the first priority. A brace or corset can help stabilize the spine or other areas, reducing movement and pain. Moderate exercise is also important in recovering bone strength and mobility and can help in overall pain reduction.

**Bone-Modifying Agents (BMAs)** – BMAs, which include both bisphosphonates and the newly approved RANK ligand inhibitor, Xgeva (denosumab), are an essential component of supportive care for patients with myeloma.

Bisphosphonates are a class of chemicals that bind to the surface of damaged bones in patients with myeloma. This binding inhibits ongoing bone destruction and can improve the chances of bone healing and recovery of bone density and strength. A randomized study utilizing the bisphosphonate pamidronate (Aredia) showed particular benefit in patients responding to ongoing chemotherapy. The IMWG's 2013 recommendations for the treatment of myeloma-related bone disease state that bisphosphonate therapy should be considered in all patients receiving first-line anti-myeloma therapy, regardless of the presence of osteolytic bone lesions on conventional radiography. Other bisphosphonates available include zoledronic acid, approved in the US and Europe as treatment of both hypercalcemia and bone disease, and clodronate, an oral formulation in use in Europe for the treatment of myeloma bone disease. The UK's phase III MRC Myeloma IX clinical trial

demonstrated both the benefit of bisphosphonate therapy in patients with newly diagnosed myeloma who did not have lytic bone disease, as well as the superiority of Zometa over clodronate.

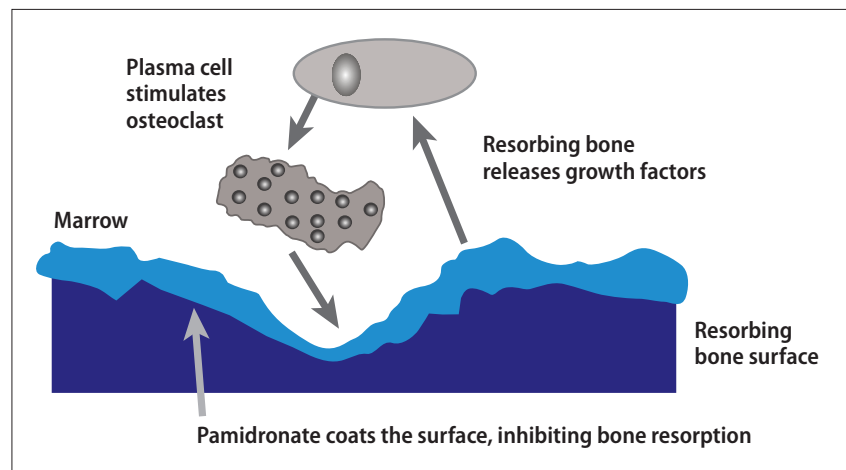
Several concerns have emerged related to chronic bisphosphonate use. Two of these, kidney damage and osteonecrosis of the jaw (ONJ) are addressed in detail in the IMF publication *Understanding Treatment of Myeloma Bone Disease*. Both conditions are fortunately relatively uncommon, but awareness of these potential problems is the key to prevention. Kidney function must be serially monitored (especially serum creatinine before each treatment dose), particularly with Zometa use. If the serum creatinine increases by 0.5 to 1.0 mg/dL, dose and/or schedule adjustments for Aredia or Zometa may be required. For Zometa, one of the simplest adjustments is to extend the infusion time from 15 minutes to 30–45 minutes, which reduces the risk of renal impairment.

Xgeva, now approved in both the US and Europe for the prevention of skeletal-related events in patients with myeloma, demonstrated its non-inferiority to Zometa in the pivotal 1,718-patient phase III '482 study. Unlike the bisphosphonates, Xgeva is not excreted through the kidneys. The 2018 ASCO clinical practice guideline update on bone-modifying agents in myeloma (Anderson et al., *JCO*, 2018) states that "fewer adverse events related to renal toxicity have been noted with denosumab compared with zoledronic acid and may be preferred in this setting."

Like the bisphosphonates, however, denosumab can cause ONJ and is mentioned along with other anti-bone resorption agents in the American Academy of Oral Medicine (AAOM) updated 2014 position paper on the management of bisphosphonate-related ONJ (BRONJ). The AAOM's first recommendation is prevention of medicine-related ONJ through regular dental check-ups. If a problem is found, referral to an expert (i.e., an oral surgeon) is strongly recommended. Any major jaw surgery must be avoided until consultation has been sought. Dental extractions should be avoided until full consultation has been obtained as well. Infection may require antibiotic therapy. In recent years, the incidence of ONJ appears to have decreased dramatically in the wake of greater awareness of the problem and attention to dental hygiene before and after initiating bisphosphonate therapy.

Additional concerns have emerged with long-term use of BMAs. Although atypical (subtrochanteric) fractures of the femur are rare, there is data that establishes an association with five or more years of bisphosphonate treatment with their occurrence. These fractures have occurred in clinical trials with denosumab as well. The FDA has included

**Figure 7. How pamidronate works**



subtrochanteric fracture of the femur to the “Precautions and Warnings” section of the package inserts for all BMAs, including Xgeva.

The IMWG’s 2013 recommendations state that for patients in CR or VGPR, the optimal duration of bisphosphonate therapy is not clear; bisphosphonates should be administered for at least 12 months and up to 24 months, and then at the physician’s discretion. For patients who have active disease, who have not achieved a response, or who have threatening bone disease beyond two years, bisphosphonate therapy can be decreased to every three months. The current ASCO guidelines recommend treating monthly for up to two years, with less frequent dosing considered in patients with responsive or stable disease. Discontinuation of bisphosphonates for patients whose disease is responsive or stable should be considered after two years. The drug should be resumed if relapse occurs with new skeletal-related events.

The ASCO guidelines warn that **denosumab should not be stopped abruptly**, given its reversible mechanism of action. The Xgeva package insert warns of multiple vertebral fractures (MVF) following treatment discontinuation, and counsels the treating doctor to “evaluate the individual patient’s risk for vertebral fractures.” Physicians are also advised to counsel their female patients that Xgeva can cause embryo-fetal harm.

**Antibiotics** – Infections are a common and recurrent problem in patients with myeloma. A careful strategy for infection management is required. Antibiotic therapy should be instituted immediately if active infection is suspected.

Use of preventive or prophylactic antibiotics with recurrent infection is controversial. A comparative study (URCC/ECOG, DH Vesole et al.) presented at ASH 2010 concluded that “the use of prophylactic antibiotics did not decrease the incidence of serious infection (> grade 3 and/or hospitalization) nor of any infection within the first two months of treatment.” Based on this study, the authors recommend that antibiotics should not be mandated in the first two months of treatment, but should be considered on a case-by-case basis. The continuation of prophylactic antibiotics can increase the chance of antibiotic resistance, but it can also reduce the chance of recurrent infectious complications. This matter was re-examined in the large UK “Tracking Early Morbidity and Mortality in Myeloma” clinical trial presented at ASH in 2017. This 977-patient study showed that there is a significant benefit for the use of 12 weeks of levofloxacin, a quinolone antibiotic, in reducing episodes of fever and deaths without increasing healthcare-associated infections (usually from hospital-borne pathogens such as MRSA and *c. difficile*).

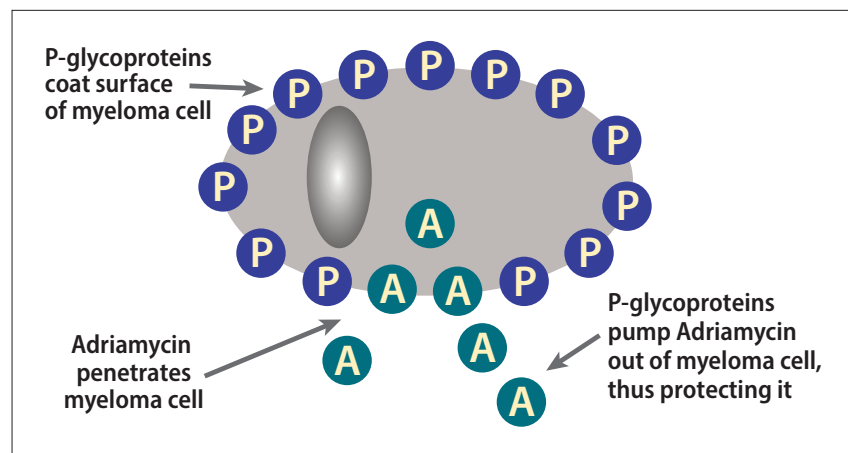
The use of high-dose gammaglobulin therapy may be required in patients with acute and severe recurrent infections. GM-CSF may be helpful in improving the white blood cell levels in an effort to overcome infectious complications. The use of G-CSF or GM-CSF is helpful in the recovery phase following bone marrow or stem cell transplantation. G-CSF and GM-CSF are also used in harvesting stem cells.

**Antivirals** – An increased incidence of herpes zoster (shingles) has been observed in some patient populations with myeloma (but not other malignancies) who are treated with proteasome inhibitors and the monoclonal antibody Darzalex. **Therefore, prophylactic antiviral therapy should be considered with all proteasome inhibitors and with Darzalex. Myeloma patients are cautioned not to get the Zostavax® shingles vaccine, as it is a live virus that poses a significant risk to those who are immunocompromised.** While the newly approved Shingrix® vaccine is not made from a live virus, and is recommended even for those who have already had Zostavax, it has not been tested in severely immunocompromised adults. Myeloma patients should consult their oncologists about use of Shingrix.

## Relapsing or refractory disease

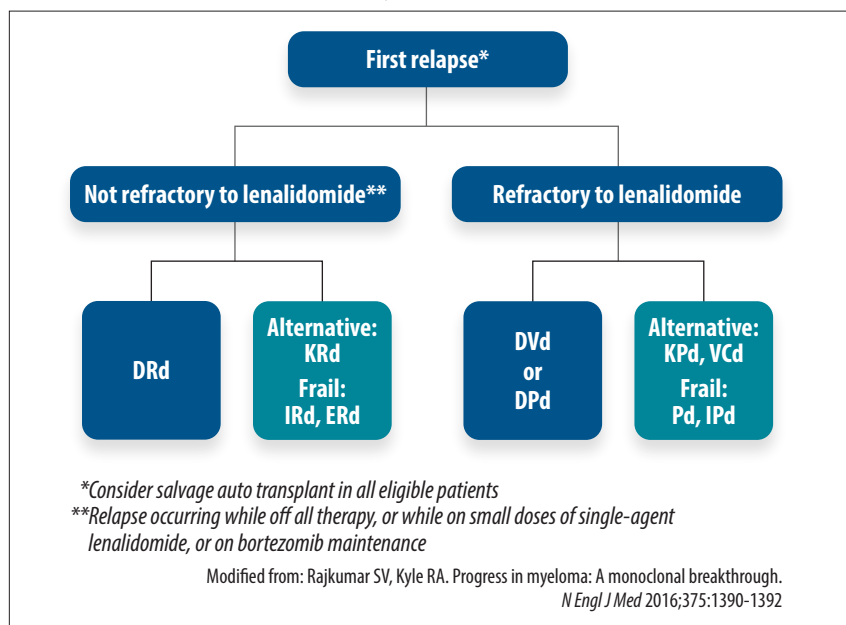
As illustrated in the pathophysiology section, a frequent problem in myeloma is the relapse that occurs following a one- to three-year remission. Although maintenance therapy may be useful in prolonging the initial remission period, the relapse, which supervenes inevitably, requires re-induction therapy. The following is an overall strategy for the management of relapsing disease.

**Figure 8. Multi-Drug-Resistant (MDR) myeloma cell**





**Figure 9. Myeloma: first relapse**



If first relapse occurs after a remission of at least six months to one year, the first strategy is to consider re-utilizing the therapy that produced the remission in the first place. NCCN guidelines state that “if the relapse occurs greater than six months after completion of the initial primary therapy, patients may be retreated with the same primary regimen.” Approximately 50% of patients will experience a second remission with the same therapy that produced the first. This is particularly true for patients whose disease is in remission for more than one year following the initial induction attempt.

Dr. Rajkumar’s treatment algorithm for first relapse reflects decision-making based on response to first therapy. See accompanying Figure.

**Velcade (bortezomib)** plays a crucial role as a platform on which to base combination therapies for relapse (VR, VRD, VCD, etc.). In August 2014, based on the international phase II RETRIEVE clinical trial, bortezomib was approved in the US for the retreatment of adult patients with myeloma who had previously responded to bortezomib therapy and relapsed at least six months following completion of that therapy.

**Kyprolis (carfilzomib)** has been evaluated alone and as a backbone drug in combination therapy clinical trials for relapse therapy. It has demonstrated safety and efficacy in such combination therapies as KCyD,

KRD, KTD, and KCyTD, all of which were presented at ASH in 2012. Final results of the ASPIRE clinical trial comparing carfilzomib + Revlimid + dexamethasone to Revlimid + dexamethasone in relapsed myeloma were presented at the 2014 annual ASH meeting, demonstrating the superiority of KRD over RD. Second interim results of the ENDEAVOR clinical trial comparing carfilzomib + dexamethasone to bortezomib + dexamethasone in myeloma patients who had had from one to three prior therapies were published in August 2017, and demonstrated that median overall survival was 47.6 months in the carfilzomib group versus 40.0 months in the bortezomib group. Grade 3 or worse adverse events were more frequent in the carfilzomib-treated patients (16% versus 10%), and there were 5 treatment related deaths (out of 463 patients) in the carfilzomib arm versus 2 treatment-related deaths (out of 456 patients) in the bortezomib arm.

Final analysis of this clinical trial, and of other studies going forward with carfilzomib, will have to determine whether the higher-than-approved dose of carfilzomib in the ENDEAVOR clinical trial (20/mg/m<sup>2</sup> versus the approved 20/27 mg/m<sup>2</sup>) and the number of patients in the clinical trial who had had previous bortezomib significantly influenced the results. The results of the phase I carfilzomib + pomalidomide + dexamethasone clinical trial in relapsed/refractory myeloma were published in *Blood* in November 2015. The data showed that the combination was well tolerated and highly active, with a 50% response rate (PR or better) in highly pretreated patients.

**Pomalyst (pomalidomide)** has also demonstrated its value in the relapse setting in multiple combination therapy clinical trials (PD, PVD, PCyPred, BiaxinPD, PCyD, KPD). Encouraging recent news from the IFM was published in *Blood* in February 2015, indicating that patients with early relapsed/refractory myeloma who have high-risk deletions 17p and/or t(4;14) show improved PFS and OS with pomalidomide + low-dose dexamethasone.

The approval of **Darzalex (daratumumab)** was the most eagerly anticipated among the late-2015 FDA approvals of panobinostat (Farydak®), daratumumab, ixazomib (Ninlaro), and elotuzumab (Empliciti). These agents provide new options for the treatment of patients with relapsed disease. The optimal sequencing and combining of therapies remains to be sorted out. Of these approved therapies, only Darzalex (daratumumab) has shown single-agent activity and may be administered as monotherapy to patients who have received at least three prior therapies, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory. The approval of

**Table 12. Myeloma: second or higher relapse**

<b>Consider Other First Relapse Options</b>	
• Daratumumab-based: DRd, DVd, DPd	• Elotuzumab-Rd
• Carfilzomib-based: KRd, KPd	• VCD, Pom-dex, Ixa-Pd
• Ixazomib-Rd	
<b>Additional Options</b>	
• Quadraplets/multi-drug chemo	• Bendamustine
• Panobinostat-Bortez-Dex	• IV melphalan
<b>Always Consider Clinical Trials</b>	
Especially CAR-T, anti BCMA ab, etc	

Rajkumar SV. 2017

daratumumab monotherapy was rapidly followed by US and EU approvals of daratumumab + bortezomib + dexamethasone in patients who have had at least one prior therapy, and of daratumumab + lenalidomide + dexamethasone in patients with relapsed or refractory myeloma in 2016. In late 2017, the FDA approved daratumumab + pomalidomide + dexamethasone for the treatment of myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. These approvals have broadened the relapse indications for daratumumab. Clinical trials with daratumumab in the relapsed/refractory setting, including subcutaneously administered daratumumab, daratumumab + KPd, daratumumab + CyBorD, and daratumumab in combination with other experimental agents, are ongoing.

Panobinostat was approved in combination with bortezomib and dexamethasone for patients who have had at least two prior regimens, including bortezomib and an immunomodulatory drug; ixazomib and elotuzumab were approved in combination with lenalidomide and dexamethasone, the former for patients who have had one prior therapy, and the latter for patients who have had one to three prior therapies. Issues of cost, value, and access to expensive combination therapies with these new drugs remain to be sorted out.

Dr. Rajkumar's algorithm for treatment of second or higher relapse includes both three- and four-drug regimens. Please see Table 12.

**Other options** – It is important to keep in mind that a variety of single and combination chemotherapy protocols are available for the management of relapsing and refractory disease. Depending upon the exact problem, a variety of interventions may be possible. For example,

if relapse is associated with the development of one or two bone lesions, radiation to the site(s) of bone involvement may be a satisfactory way to manage the relapse. If overall relapse has occurred, dexamethasone as a single agent can be very useful in achieving overall control of the disease. The use of dexamethasone is attractive because it can be given by mouth and does not cause significant side effects such as hair loss or reduction in peripheral blood count values.

Another important point is that relapse following high-dose therapy with transplant has, in many cases, a pattern similar to relapse following more standard approaches. Second and sometimes third remissions can be achieved following relapse after bone marrow transplantation. Patients who have had durable remissions to a first transplant of at least two years may consider doing a second transplant at relapse. Whether a second high-dose therapy with transplant is the most appropriate strategy, as opposed to some other approach, is currently unclear and must be based upon individual patient considerations.

Given the continuing rapid rate of development of new therapies for myeloma, as well as investigation of new combinations of existing and new agents, treatment in the context of clinical trials can be an option for patients with relapsed myeloma.

## New and emerging therapies

Many new treatments and combination therapies are available in the setting of clinical trials. Clinical trial phases are listed in the accompanying Table. The emergence of immunotherapy has created a new paradigm in cancer treatment; immuno-oncology agents currently in clinical trials for myeloma include monoclonal antibodies, antibody-drug conjugates (ADC), bispecific T cell engagers (BiTe), CAR T-cell therapies, engineered dendritic cells, oncolytic virotherapies, and vaccines.

Concerns have arisen about the use of another type of immune-oncology agent, however. Checkpoint inhibitors have already been approved for the

**Table 13. Clinical trial phases**

<b>I</b>	Early testing to assess dosing, tolerance, and toxicity in patients
<b>II</b>	Further testing to evaluate how effective treatment is at the dose and schedule selected
<b>III</b>	Comparison of the new treatment with prior treatment(s) to determine if the new treatment is superior
<b>IV</b>	Usually carried out after FDA approval to assess cost-effectiveness, quality of life impact, and other comparative issues

treatment of some advanced solid tumors, but have not yet demonstrated safety and efficacy in patients with relapsed/refractory myeloma. The FDA halted two clinical trials in which the checkpoint inhibitor pembrolizumab was combined with an immunomodulatory agent, noting both lack of efficacy and poorer overall survival.

A drug that is under accelerated evaluation by the FDA for treatment of “penta-refractory” myeloma (i.e. refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab) has a new mechanism of action. It is a “selective inhibitor of nuclear export,” preventing myeloma cells from ridding themselves of tumor suppressor genes in their nuclei.

Patients are encouraged to check with their physicians regarding the availability of new clinical trials. For questions or concerns, the IMF is available via email at [TheIMF@myeloma.org](mailto:TheIMF@myeloma.org) or by calling 800-452-CURE, toll-free in the United States and Canada, or 818-487-7455 from other parts of the world. The *Myeloma Matrix 2.0: Smart Patients*, the IMF search tool that lists all drugs currently in clinical trials for myeloma, is available with ongoing updates on the IMF website at [matrix.myeloma.org](http://matrix.myeloma.org). Good summaries of new therapies are presented in the IMF reports from ASH, ASCO, IMWG, and the European Hematology Association (EHA). These summaries are available online at [myeloma.org](http://myeloma.org) or by calling the IMF.

## Recommended reading

### 2017

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## You are not alone. The IMF is here to help.

Myeloma is a cancer that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments.

The IMF produces and maintains a library of publications to help arm you with one of the most important weapons in the fight against myeloma: INFORMATION. The following is a partial list of publications available in English, and selected titles are also available in other languages.

- *Patient Handbook*
- *Concise Review of the Disease and Treatment Options*
- *Understanding Clinical Trials*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding DARZALEX® (daratumumab)*
- *Understanding EMPLICITI® (elotuzumab)*
- *Understanding Fatigue*
- *Understanding High-Dose Therapy with Stem Cell Rescue*
- *Understanding the Immune System in Myeloma*
- *Understanding KYPROLIS® (carfilzomib)*
- *Understanding MGUS and Smoldering Multiple Myeloma*
- *Understanding NINLARO® (ixazomib) capsules*
- *Understanding POMALYST® (pomalidomide)*
- *Understanding REVLIMID® (lenalidomide)*
- *Understanding Treatment of Myeloma Bone Disease*
- *Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures*
- *Understanding VELCADE® (bortezomib)*
- *Understanding Your Test Results*

All IMF publications and periodicals are always free of charge. Visit **publications.myeloma.org** to read, download, or order printed copies. Subscribe to IMF periodicals at **subscribe.myeloma.org** or by contacting the IMF.

As always, the IMF urges you to discuss all medical issues with your doctor, and to contact the IMF's InfoLine specialists with your myeloma questions and concerns.

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