



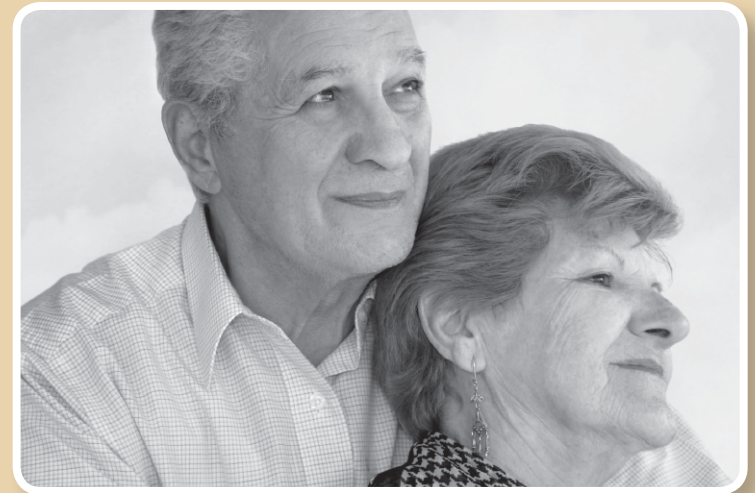
International Myeloma Foundation
12650 Riverside Drive, Suite 206
North Hollywood, CA 91607-3421
Hotline (USA & Canada): (800) 452 CURE (2873)
Tel: (818) 487-7455
Fax: (818) 487-7454
Email: TheIMF@myeloma.org
Website: myeloma.org

*Dedicated to improving the quality of life
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Concise Review

of the Disease and Treatment Options



Multiple Myeloma

Cancer of the Bone Marrow



International Myeloma Foundation
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Prepared by Brian G.M. Durie, MD

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INTRODUCTION

The IMF Concise Review of the Disease and Treatment Options is an overview of myeloma, with a discussion of the pathophysiology, clinical features, and treatment options. It is hoped that the information will be helpful to health professionals and patients alike.

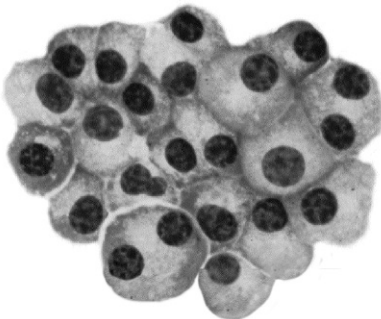
WHAT IS MYELOMA?

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 (*see Figure 1*) 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 surrounding the bone marrow cavity
- Production and release of monoclonal protein (M-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 (extramedullary or soft tissue). When there are multiple plasmacytomas inside or outside bone, this condition is also called multiple myeloma.

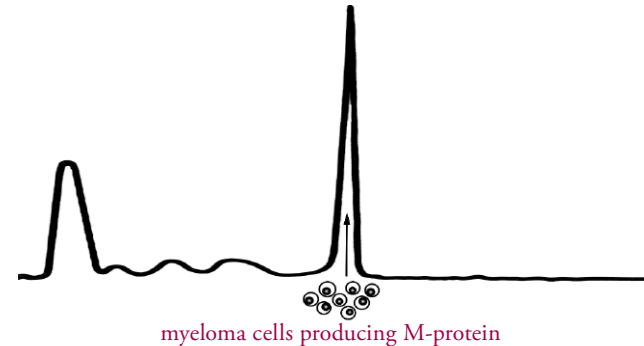
FIGURE 1: MYELOMA CELLS



PRODUCTION OF MONOCLONAL PROTEIN BY MYELOMA CELLS

The characteristic property of myeloma cells is the production and release (or secretion) 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 even 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, or the 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 (*see Figure 2*).

FIGURE 2: MONOCLONAL SPIKE

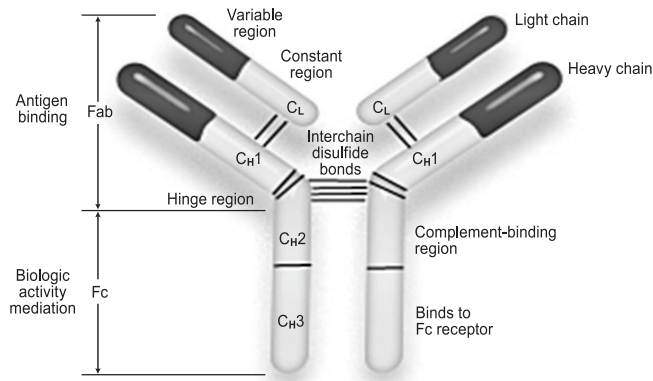


The monoclonal protein is an immunoglobulin or a component/fragment of an immunoglobulin. Figure 3 illustrates the structure of a normal immunoglobulin molecule. In myeloma cells, one or more mutations have occurred in the genes responsible for immunoglobulin production. Myeloma proteins therefore have 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.

Increased production of abnormal immunoglobulin has a number of consequences:

- **Excess M-protein accumulates** in the bloodstream and/or is excreted in the urine as a monoclonal spike.
- **The abnormal monoclonal molecules can adhere** to each other and/or other tissues such as blood cells, blood vessel walls, and other

FIGURE 3: IMMUNOGLOBULIN MOLECULE STRUCTURE



• **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. **Amyloidosis** – A disease entity in which the Bence Jones light chains crosslink in a highly symmetric, β -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)** – The light chains are deposited in a more haphazard fashion, but most especially in small blood vessels of the eyes and kidneys; or
3. **Monoclonal Immunoglobulin Deposition Disease (MIDD)** – A disease in which there is deposition of fragments of 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 interference with chemical reactions.

blood components. This can reduce blood flow and circulation, causing hyperviscosity syndrome (*discussed below*).

- **Approximately 30% of the time, 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 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
 - Binding to nerves to cause neuropathy or to circulating hormones to cause metabolic dysfunction.

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 on boiling, but re-precipitated on cooling: what are now called “Bence Jones” light chains. This patient also had a very strange bone disease that we now call myeloma. The following is a brief annotated summary of progress in research and treatment for multiple 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 Dr. William Macintyre in London. The unusual urine problem he discovered was fully investigated by Dr. Henry Bence Jones, who published his findings in 1848. In 1846, Mr. John Dalrymple, a surgeon, determined that the diseased bones contained cells subsequently shown to be plasma cells. Dr. Macintyre published the full details of this case of Bence Jones myeloma in 1850. Dr. Samuel Solly published a similar case of myeloma (Sarah Newbury) in 1844, but without any detailed urine studies.

1873 Rustizky introduced the term “multiple myeloma” to designate the presence of multiple plasma cell lesions in bone.

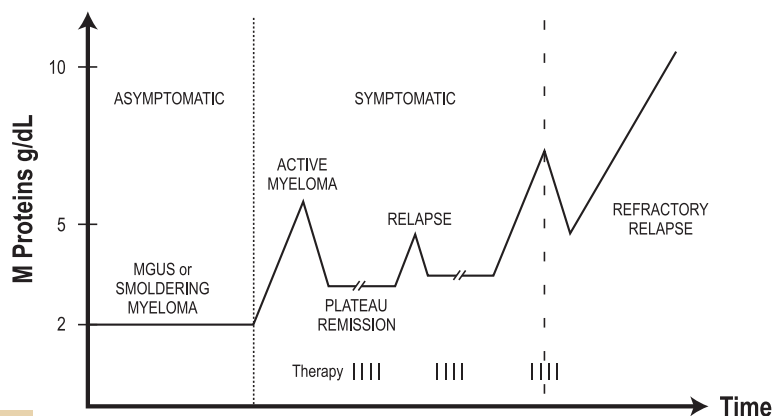
1889 Otto Kahler published a detailed clinical description of multiple myeloma, “Kahler’s disease.”

1890 Ramon y Cajal provided the first accurate microscopic description of plasma cells.

1900 Wright discovered that multiple myeloma cells are plasma cells.

1903 Weber noted that myeloma bone disease (lytic lesions) is detectable using X-rays.

FIGURE 4: DISEASE PHASES



- 1909 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 Korngold and Lipari noted that Bence Jones (BJ) 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 or L).
- 1958 Discovery of sarcolysin in the USSR. From this, melphalan (Alkeran[®]) was derived. For the first time, treatment was possible.
- 1961 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 (Alkeran[®]) by Bergsagel.
- 1964 First report of successful treatment of myeloma with cyclophosphamide (Cytosan[®]) by Korst. Results with cyclophosphamide proved to be similar to results with melphalan.
- 1969 Melphalan combined with prednisone was shown by 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 (Gregory) showed equivalent results for all combinations.
- 1979-1980 Labeling index (growth fraction analysis) first introduced as a test in myeloma and related diseases. Stable remission or plateau phase of myeloma identified. Plateau phase is a period when the growth fraction (LI%) of residual bone marrow plasma cells is zero.
- 1982 Twin transplants performed by Fefer and Osserman as treatment for myeloma.
- 1983 First use of serum β 2 microglobulin as a prognostic test (Bataille, Child, and Durie).
- 1984 Barlogie and Alexanian introduce VAD chemotherapy.
- 1984-1986 First reports of allogeneic transplants in multiple 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 (McElwain) and double (Barlogie) transplant procedures introduced.
- 1996 First randomized study indicating possible benefit of high-dose therapy with bone marrow transplant support versus standard chemotherapy (Attal).
- 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 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-vs-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 2 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., 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., VELCADE[®]).
- 2001 New classification system proposed for myeloma and related diseases (*see Table 1 below*).
- IFM (French Study Group) defines 3 risk groups based upon serum β 2 microglobulin and presence/absence of abnormalities of chromosome 13 by FISH analysis.
- 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%.
- MRC in U.K. reports autotransplant results at ASH (American Society of Hematology) annual meeting. Overall benefit noted, especially for patients with high serum β 2 microglobulin (>7.5 mg/L).

- 2003 VELCADE® (bortezomib; formerly PS-341) approved by the FDA as treatment for actively relapsing myeloma following at least 2 prior therapies. MRC autotransplant results provide the second randomized data set indicating benefit of autotransplant versus standard-dose chemotherapy. Results of IFM study comparing single with double transplant published showing overall benefit with the double transplant after more than four years of follow-up. However, no apparent added benefit for patients already in complete remission with the first transplant. Little Rock group (Shaugnessy/Barlogie) shows that bone disease in myeloma is associated with production of a particular protein called DKK-1.
- 2004 Results of 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 multi-institutional randomized trial comparing VELCADE® with dexamethasone show superiority of VELCADE® (details discussed in text). Early results with VELCADE® in the frontline setting show excellent results: 83% response rate for 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 ISS (International Staging System). *See page 17.*
- 2005 Two large Phase III trials show that Revlimid® (lenalidomide) plus dexamethasone is superior to dexamethasone alone in relapsed myeloma (time to progression >15 months vs. 5 months). VELCADE® receives full FDA approval for treatment of patients with myeloma after 1 prior therapy. International Staging System (ISS), developed by the International Myeloma Working Group (IMWG) of the International Myeloma Foundation (IMF), is published (*see page 17*). Numerous new agents in early development. Heat shock protein (HSP)-90 inhibitors enter Phase I-II trials. 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. Revlimid® receives FDA approval for treatment of myeloma in combination with dexamethasone in patients who have received at least 1 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 1 prior therapy. Combination thalidomide/dexamethasone plus Doxil® compared with thalidomide/dexamethasone in a phase III trial for newly diagnosed myeloma.

New agents in development include: HSP-90 inhibitors, new proteasome inhibitors, and new immunomodulatory agents. Evidence emerges that some novel therapies may overcome some high-risk factors.

- 2008 Thalidomide approved by the EMEA in Europe as part of the “MPT” regimen (melphalan/prednisone/thalidomide) for frontline therapy. VELCADE® approved by the FDA in the US 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) shows promise in early trials.
- Mozobil® (plerixafor) approved 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 tanespimycin; monoclonal antibody elotuzumab; and third-generation immunomodulatory agent pomalidomide.
 - IMWG analysis shows cytogenetic and FISH abnormalities combined with ISS stage are prognostic; some novel therapies overcome poor risk factors.
- 2010
- US 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 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 immunomodulatory agent pomalidomide.
 - Several studies suggest a role for lenalidomide maintenance therapy.
 - Frontline therapy with novel agents may be as effective as transplantation in eligible patients.
 - Zometa® (zoledronic acid) may have an anti-myeloma effect; effective dental hygiene has reduced occurrence of ONJ.

EPIDEMIOLOGY

The average incidence of myeloma is 3-4/100,000 in the US, representing approximately 1.3% of all types of cancer. The American Cancer Society estimated that in 2010, approximately 20,180 Americans would be diagnosed with myeloma, and 10,650 people would die from the disease. (Estimates for 2011 are not available at the time of this writing.) There are currently approximately 100,000 Americans undergoing treatment for the disease. Myeloma is more common in African Americans than Caucasians. For example, in Los Angeles County the incidence of myeloma in African American men is

TABLE 1

Definitions of Myeloma and Related Monoclonal Gammopathies

NAME	DEFINITION
MGUS (Monoclonal Gammopathy of Undetermined Significance)	<ul style="list-style-type: none"> • Monoclonal protein present • No active plasma cell disorder
ASYMPTOMATIC or SMOLDERING MYELOMA	<ul style="list-style-type: none"> • Higher level of disease than MGUS, but still no symptoms or organ damage • Can be classified into low or high risk based upon lesser or greater chance of transition to active myeloma
SYMPTOMATIC or ACTIVE MYELOMA	<ul style="list-style-type: none"> • Monoclonal protein present, and • One or more “CRAB” features of organ damage present*

*Organ damage classified as “CRAB”

C – calcium elevation (> 10 mg/L)

R – renal dysfunction (creatinine > 2 mg/dL)

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

B – bone disease (lytic lesions or osteoporosis)

ONE OR MORE required for diagnosis of SYMPTOMATIC MYELOMA.

Other less common features can also be criteria for an individual patient, including:

- Recurrent severe infections
- Neuropathy linked to myeloma
- Amyloidosis or M-component deposition
- Other unique features

9.8/100,000 versus 4.3/100,000 for Caucasian men. The incidence varies from country to country from a low of <1/100,000 in China to approximately 4/100,000 in most Western industrialized countries. The male:female ratio is 1.25:1 in the US. The incidence rises with age. 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 in the past 60 years. Several recent studies have evaluated the causation of, or predisposition to myeloma, MGUS, and related disorders. Firefighters and individuals in a variety of other occupations with toxic exposure as well as individuals who are obese are at increased risk of myeloma. Eating seafood contaminated with heavy metals and/or chemicals may be a 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, and renal insufficiency. Nonetheless, the disease can remain asymptomatic for many years, as noted in the discussion of MGUS. In the symptomatic phase, the most common presenting complaint 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, which are not quite identical, but are used synonymously). The overall pattern of disease phases for patients with myeloma is illustrated in Figure 4. It is important to note that there can be multiple periods of response and remission. The pathophysiology of myeloma is summarized in Table 2 in schematic form.

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 has evolved from the observation that myeloma cells produce osteoclast-activating factors (OAFs) to the identification of local cytokines such as IL-1 β , IL-6, and TNF- α and - β ; chemokines such as MIP-1 α ; and cell-cell adhesion processes involving α v β 3 integrin, all of which are involved in producing increased numbers and activity of osteoclasts. More recently a substance called RANK ligand (RANKL) has been identified as a critical mediator of osteoclast activation. Many details of the mechanisms of bone disease in myeloma are now understood. Several targets for treatment approaches have been identified.

Besides activation of osteoclasts, the other characteristic feature of myeloma bone disease is 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 also under investigation. An important new observation is that the cholesterol-lowering statins (HMG-CoA reductase inhibitors, e.g., Lipitor®, Mevacor®), can enhance osteoblast activity and promote bone healing. In addition, both VELCADE® and lenalidomide (Revlimid®) have been shown to promote bone healing, in addition to exerting a 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 cytokine and adhesion molecule effects is a more functional explanation. The exact causes of myeloma-related anemia are being investigated by several research teams.

TABLE 2
Schema of Pathophysiology

Skeletal Findings

- Solitary or multiple osteolytic lesions
- Diffuse osteoporosis (osteopenia)

Associated Effects Of Bone Destruction

- Elevated serum calcium
- Hypercalciuria (calcium increase in urine)
- Bone fractures
- Loss of height (vertebral collapse)

Extraskeletal Myeloma (Rare)

- Soft tissue involvement, most commonly in head/neck area (e.g., nasopharynx); also in liver, kidney, and other soft tissue sites

Peripheral Blood

- Anemia
- Abnormal clotting
- Leukopenia
- Thrombocytopenia
- Plasma cell leukemia
- Circulating monoclonal B lymphocytes (precursors of myeloma cells)

Plasma Protein Changes

- Hyperproteinemia (elevated protein)
- Hypervolemia (expanded volume)
- Monoclonal immunoglobulins (IgG, IgD, IgA, IgM, IgE, or light chains only)
- Narrowed anion gap (low serum sodium)
- Elevated serum β 2-microglobulin
- Decreased serum albumin
- Elevated serum IL-6 and C-reactive protein (CRP)

Kidney Abnormalities

- Proteinuria, casts without leukocytes or erythrocytes
- Tubular dysfunction with acidosis
- Uremia (kidney failure)
- Amyloidosis and renal dysfunction

Improvement in anemia occurs with successful treatment of the myeloma. Recombinant erythropoietin (Epo) (e.g., Epogen® or Procrit®) should be used with caution in the light of recent reports of the association of Epo with increased tumor growth and reduced survival in patients with cancer, and the identification of Epo receptors on myeloma cells.

KIDNEY DYSFUNCTION

Impairment of kidney function is a common complication in patients with myeloma. However, this does not mean that 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 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 cause metabolic bone disease.

Other important factors related to kidney dysfunction in multiple myeloma patients are 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. An important new observation is the potentially toxic effect of gadolinium-based contrast agents used with MRI. Patients with kidney problems should discuss the use of gadolinium with their physicians. Awareness of potential kidney damage and maintaining 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.

- **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 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 primary nerve disorders such as multiple sclerosis, Parkinson's disease, and many 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 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 and require 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 but aberrant monocyte/macrophage function. Some studies indicate that a factor issuing from the activated macrophages both enhances the activity of the myeloma 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 and the effects of high-dose chemotherapy, and with the added local effects of implanted catheters (e.g., Hickman and Groshon catheters or PICC lines), the whole range of bacterial, fungal, and opportunistic infections can occur in patients with myeloma 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 is IgG and the least common is IgE. Table 3 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 collapse of a vertebral body. General malaise and vague complaints are frequent. Significant weight loss is rare.

Both neutropenia and hypogammaglobulinemia 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 diagnosis, causes tiredness, thirst, and nausea. Precipitation of calcium salts can result in deterioration of kidney function. Of note, 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 myeloma protein levels 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 (IgM paraprotein or M-component). Increased bleeding

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%	
Heavy chains (G or A) only	<1%	2%
No monoclonal paraprotein	1%	
4. IgM (rarely myeloma; typically associated with Waldenström's macroglobulemia)		12%
TOTAL		100%

*This includes different types of MGUS and myeloma as well as Waldenström's.

Source: Data on 1,827 myeloma patients collected and analyzed by Pruzanski and Ogryzlo, 1970.

is often exacerbated by thrombocytopenia as well as by binding of monoclonal proteins to clotting factors and/or platelets.

Neurologic involvement can result in specific problems depending on the location of affected nerves. Particularly common problems are spinal cord compression, meningitis, and carpal tunnel syndrome. Although the first two are due to plasma cell tumor formation or infiltration, carpal tunnel syndrome is usually due to amyloid deposition (deposition of Bence Jones proteins in a special β -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 (see Table 4). This system brings together the major clinical parameters in correlation with measured myeloma cell mass (the total number of myeloma cells in the body). The Durie/Salmon staging system continues to be used worldwide, primarily because it provides the best direct correlation with individual patient clinical features. Stage I patients have smoldering disease; Stage II and III patients have active myeloma. In 2005, a new staging system was developed by the IMF-sponsored International Myeloma Working Group (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 β_2 microglobulin (S β_2 M), serum albumin, platelet count, serum creatinine, and age emerged as powerful predictors of survival and were then further analyzed.

A combination of serum β_2 microglobulin and serum albumin provided the most, powerful, simple, and reproducible three-stage classification. This International Staging System (ISS) was fully validated and is shown in Table 5. 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 system. The ISS is simple, based upon easy-to-use variables (serum β_2 M and serum albumin), and has been introduced for widespread use.

Myeloma can be further classified based upon genetic risk using molecular fluorescence in situ hybridization (FISH) and cytogenetic features identified in bone marrow myeloma cells. Such classification can have important implications for treatment. Higher-risk disease is defined as the presence of any

TABLE 4
Durie and Salmon Staging System

CRITERIA	MEASURED MYELOMA CELL MASS (myeloma cells in billions/m ²)*
STAGE I (low cell mass) All of the following: <ul style="list-style-type: none"> • Hemoglobin value > 10 g/dL • Serum calcium value normal or < 10.5 mg/dL • Bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only • Low M-component production rates IgG value < 5.0 g/dL IgA value < 3.0 g/dL Urine light chain M-component on electrophoresis < 4 g/24h 	600 billion myeloma cells*
STAGE II (intermediate cell mass) Fitting neither stage I nor stage III	600 to 1,200 billion myeloma cells*
STAGE III (high cell mass) One or more of the following: <ul style="list-style-type: none"> • Hemoglobin value < 8.5 g/dL • Serum calcium value > 12 mg/dL • Advanced lytic bone lesions (scale 3) • High M-component production rates IgG value > 7.0 g/dL IgA value > 5.0 g/dL Urine light chain M-component on electrophoresis > 12 g/24h 	> 1,200 billion myeloma cells*
SUBCLASSIFICATION (either A or B) <ul style="list-style-type: none"> • A: relatively normal renal function (serum creatinine value) < 2.0 mg/dL • B: abnormal renal function (serum creatinine value) > 2.0 mg/dL 	

Examples: Stage IA (low cell mass with normal renal function)

Stage IIIB (high cell mass with abnormal renal function)

*myeloma cells in the whole body

one of the following genetic mutations: t(4;14), t(14;16), t(14;20), deletion of 17p by FISH, or deletion of chromosome 13 or hypodiploidy by conventional metaphase cytogenetics. It is crucial to be aware that genetic risk is very much influenced by the treatment selected. For example, the deletion of 17p by FISH is the only factor that consistently correlates with poorer outcomes with all therapies available in 2011. Conversely, the presence of t(4;14), which has been noted as a poor risk factor in the past, has largely been overcome with

the introduction of VELCADE® (bortezomib) combination regimens. There is also a positive impact of lenalidomide- (Revlimid®) containing regimens in patients with t(4;14) in several Revlimid® trials. A recent report from the French IFM group indicated that the presence of t(14;16) was also no longer a predictive prognostic factor in their trials. It is anticipated that new and better risk classification systems will be introduced over time and it will become possible to offer treatment selection based upon documented treatment outcomes with new combination approaches.

**TABLE 5:
International Staging System (ISS)**

STAGE	VALUES
STAGE 1	$\beta 2M < 3.5$ ALB ≥ 3.5
STAGE 2	$\beta 2M < 3.5$ ALB < 3.5 or $\beta 2M 3.5 - 5.5$
STAGE 3	$\beta 2M > 5.5$

Note: $\beta 2M$ = Serum $\beta 2$ microglobulin in mg/L
ALB = Serum albumin in g/dL

DEFINITION OF CLINICAL RESPONSE

The new International Myeloma Working Group (IMWG) uniform response criteria are recommended to classify response (see Table 7). 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 often may not, have any tendency for immediate regrowth (relapse). If there is no re-growth, this is what 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 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 3 to 6 months (rapid response), to 12 to 18 months (slow response). Please refer to Figure 4 on page 3.

As treatments have 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 ($\geq 50\%$ improvement) or VGPR ($\geq 90\%$) (see Table 7), one must consider duration or length of response.

Two important terms 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*.

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

TREATMENT

OVERVIEW

Please see the History section for an overview of the evolution of currently used treatments. Since melphalan was first introduced in 1962, various combination chemotherapy regimens have been utilized 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 “transplant” is a “rescue” with normal bone marrow stem cells when the stem cells in the body have been destroyed by high-dose chemotherapy (usually melphalan).

In the decades of the ‘80s and ‘90s, high-dose melphalan with stem cell rescue was one of the few techniques/treatments available to reduce myeloma tumor burden and achieve better outcomes. With the introduction of thalidomide for myeloma treatment in 1997, the options suddenly changed. Complete responses could be achieved with a simple oral agent. Additional new agents followed in rapid succession: first VELCADE®, then Revlimid®, and now carfilzomib and pomalidomide, which are poised for early approval by the FDA. Other agents such as elotuzimab, vorinostat, panobinostat, and others are showing promising results.

There is no single answer to the question of “the best” treatment options available in 2011. Fortunately, there are numerous regimens that produce very deep responses (more than 90% reduction of M-component [VGPR]), durable responses (remissions lasting ≥ 2 years), and improved overall survival. The best choice for each patient depends upon individual factors such as age, stage, genetic features, kidney status, and of course personal preference. It has become an open question whether immediate auto transplant as a part of first treatment is required or whether it can be offered as an option at first relapse, for example.

It is important that myeloma patients be aware of the need for careful discussions with their physicians.

EXCLUDE MGUS OR ASYMPTOMATIC MYELOMA

The first and most important decision is to determine if treatment is required. Patients with MGUS and asymptomatic myeloma (*Table 1*) should be observed closely rather than treated. There are currently no therapies that can enhance the immune regulation of early myeloma or reduce the likelihood of disease activation. However, several research trials are ongoing to assess if early treatment is helpful in certain patients. A large cooperative group trial (combined ECOG/SWOG) was started in Fall, 2010. Patients with high-risk smoldering myeloma are randomized to Revlimid® vs. placebo. Bisphosphonate therapy can be used for patients with early bone disease. Erythropoietin could be considered for treatment of isolated anemia, keeping in mind the caveats concerning this agent.

Specific anti-myeloma treatment is recommended when symptomatic myeloma has developed, as reflected by an increasing M-component and/or emerging or imminent clinical problems or “CRAB” features (*Table 1*). 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

TABLE 6
Myeloma Treatment Options

1. Chemotherapy
2. High-dose chemotherapy with hematopoietic stem cell transplant
3. Radiation
4. Maintenance therapy
5. Supportive care:
 - Erythropoietin*
 - Bisphosphonates
 - Antibiotics
 - Exercise
 - Emergency care (e.g., dialysis, plasmapheresis, surgery, radiation)
 - Pain medication
 - Growth factors
 - Brace/corset
6. Management of drug-resistant or refractory disease
7. New and emerging treatments:
 - Thalidomide, Revlimid®, and next-generation IMiD, pomalidomide, in clinical trials
 - VELCADE® (proteasome inhibitor) and next-generation proteasome inhibitors, e.g., carfilzomib, NPI-0052, in clinical trials
 - Doxil® (pegylated liposomal doxorubicin) to substitute for Adriamycin® infusion
 - Mini-allo (non-myeloablative) transplant
 - Histone deacetylase (HDAC) inhibitors, e.g. vorinostat, panobinostat in clinical trials
 - Monoclonal antibodies in clinical trials, e.g., elotuzumab

*with caveats

myeloma protein. These indications for the need to start treatment can be summarized as CRAB features: Calcium elevation; Renal problems; Anemia; or Bone 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 Table 6, and most commonly used chemotherapeutic drugs are detailed in Table 8.

1. SYSTEMIC ANTI-MYELOMA TREATMENT:

INTRODUCTION

The first specific treatment for myeloma was melphalan, introduced in 1962. Although the use of the simple oral combination of melphalan plus prednisone is still a valid approach, several factors now influence the choice of this type of therapy.

- Melphalan can damage normal bone marrow stem cells and is therefore avoided in patients planning stem cell harvest.
- Since older age (>70 years) is not an absolute deterrent to stem cell harvest and transplant, the role of stem cell transplant must be assessed for each patient on an individual basis.

TREATMENT RECOMMENDATIONS IF STEM CELL HARVEST IS NOT A PLANNED OPTION

The approach to treatment has changed substantially with the introduction of the novel agents thalidomide, bortezomib (VELCADE®), and lenalidomide (Revlimid®). Although melphalan/prednisone (MP) is still an option for elderly patients, two new combinations with MP (*Table 9*) have emerged that are superior to MP for patients who are not eligible for transplantation: melphalan/prednisone/thalidomide (MPT), and bortezomib (VELCADE®)/melphalan/prednisone (VMP). In addition, thalidomide plus dexamethasone (Thal/Dex) and lenalidomide (Revlimid®) plus low-dose dexamethasone (RevloDex) are available for use in the non-transplant setting.

Melphalan/Prednisone/Thalidomide (MPT): NCCN (National Comprehensive Cancer Network) category 1 choice* – Three randomized trials have compared MP with MPT. Each has shown a higher response rate, longer remission, and longer progression-free survival (PFS) with MPT. Venous thrombotic event risk requires appropriate prophylaxis, depending upon individual patient characteristics. (See the International Myeloma Working Group’s

* NCCN Categories of Evidence and Consensus are: **Category 1:** the recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus; **Category 2A:** the recommendation is based on lower-level evidence and there is uniform NCCN consensus; **Category 2B:** the recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement); and **Category 3:** the recommendation is based on any level of evidence but reflects major disagreement.

guidelines for the prevention of thalidomide- and lenalidomide-related thrombosis in myeloma.)

Melphalan/Prednisone/Revlimid® (MPR): NCCN category 2A choice – Results of the ongoing Italian MM-015 study have shown that MPR confers a significant advantage in progression-free survival over MP. However, concerns have emerged about untoward toxicities, including a small risk of development of second primary cancers. This risk is currently under investigation.

TABLE 7
International Myeloma Working Group Uniform Response Criteria: CR and Other Response Categories

RESPONSE SUBCATEGORY	RESPONSE CRITERIA ^a
sCR	CR as defined below plus <ul style="list-style-type: none"> • Normal FLC ratio, and • Absence of clonal cells in bone marrow^b by immunohistochemistry or immunofluorescence^c
CR	<ul style="list-style-type: none"> • Negative immunofixation on the serum and urine, and • Disappearance of any soft-tissue plasmacytomas, and • ≤5% plasma cells in bone marrow^b
VGPR	<ul style="list-style-type: none"> • Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or • 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24h
PR	<ul style="list-style-type: none"> • ≥50% reduction of serum M-protein and reduction in 24h urinary M-protein by ≥90% or to < 200 mg per 24h • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are unmeasurable, and serum free light chain assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma percentage was ≥30% <p>In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required</p>
SD	Not meeting criteria for CR, VGPR, PR, or progressive disease (not recommended for use as an indicator of response, stability of disease is best described by providing the time to progression estimates)

Abbreviations: CR = complete response; FLC = free light chain; PR = partial response; SD = stable disease; sCR = stringent complete response; VGPR = very good partial response.

a – All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

b – Confirmation with repeat bone marrow biopsy not needed.

c – Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is a κ/λ ratio of >4:1 or <1:2.

TABLE 8
Most Commonly Used Chemotherapy Drugs

DRUG NAME	OTHER TREATMENT NAME	COMMENTS
TRADITIONAL AGENTS		
Melphalan* (M)**	Alkeran® (by mouth or IV)	First single agent for treatment of myeloma
Cyclophosphamide* (C or CY)**	Cytoxan® (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
Vincristine (V or O)**	Oncovin® (IV)	No longer commonly used as part of the VAD induction regimen, which was shown to be inferior to VELCADE® + Adriamycin® + dex
Doxorubicin (A)**	Adriamycin® (IV)	Modest activity, used in combinations (e.g., VAD, ABCM, VMCP-VBAP)
Busulphan* (B or BU)**	Myleran® (by mouth or IV)	Similar activity to M and C, usually part of high-dose therapy with transplant (e.g., BU/CY regimen)
VP - 16	Etoposide®	Modest activity, used alone or in combination
Cisplatin (CP or P)**	Platinol® (IV)	Minimal activity alone, but used with VP-16 (E) as part of combinations (e.g., EDAP and DT-PACE)
NOVEL AGENTS		
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
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

* Alkylating agents

** Common abbreviations

Bortezomib (VELCADE®)/Melphalan/Prednisone (VMP): NCCN category 1 choice – A large, randomized trial (VISTA) involving 682 patients with a median age of 71 years showed improved outcomes with VMP versus MP and resulted in FDA approval for VELCADE® in this front-line setting. Response, length of remission, and overall survival were all superior with VMP. The most important caveat is that 13% of the patients receiving VMP had severe (Grade 3 or 4) neuropathy with the VELCADE® combination. Although the neuropathy reversed in a majority of patients, this is an important concern.

Bortezomib (VELCADE®)/Melphalan/Prednisone/Thalidomide (VMPT): Not yet listed by NCCN – Weekly VELCADE® plus a reduced dose of thalidomide in combination with MP has been shown (GIMEMA trial) to result

in increased response and progression-free survival compared with VMP, with reduced rates of peripheral neuropathy and discontinuation of therapy.

Thalidomide/dexamethasone (Thal/Dex): NCCN category 2B choice and **lenalidomide (Revlimid®)/Low-Dose Dex (RevloDex):** NCCN category 1 choice – Although not tested exclusively in the nontransplant setting, both Thal/Dex and RevloDex can be considered for those who may not proceed to immediate transplant, as well as for those who are eligible for transplant.

With the approval of lenalidomide/dexamethasone (Rev/dex) in the relapse setting and with very promising trials ongoing in the frontline setting, the RevloDex combination has become a popular option for induction therapy. An important ECOG trial (E4A03) showed excellent results with Revlimid® plus low-dose (weekly) dexamethasone versus Revlimid® plus conventional-dose (4-day pulse) dexamethasone. The percentages of early side effects were very low with RevloDex, as was the chance of early mortality, which was only 0.5% (within first 4 months). RevloDex thus became an excellent option for induction. The only major caution is for patients wishing to retain the option for stem cell harvesting. Researchers at the Mayo Clinic have noted lower stem cell yields post-Rev/dex induction with a small percentage of patients not collecting adequate stem cells for transplantation using Neupogen® growth factor alone for harvesting.

At the present time, 98% of patients in the U.S. receive induction therapy that includes at least one novel agent. A recent registry survey showed that RevloDex and VELCADE®-based combinations are used in approximately equal numbers in the front-line setting, with thalidomide/dex now less frequently used.

Revlimid®/Bortezomib(VELCADE®)/Dexamethasone (RVD): NCCN category 2B choice – Trials thus far have shown very promising results for this combination. Phase III trials in the newly diagnosed and relapsed settings are ongoing. While not yet FDA approved in either the frontline or relapsed setting, this regimen is not infrequently prescribed in the United States.

A recent development of note was the French-led randomized phase III trial of subcutaneous (subq) versus IV VELCADE®, in which efficacy and toxicity were assessed. The trial determined that efficacy was equal in both trial arms, and that peripheral neuropathy of grade 2 or greater was reduced in the subq arm.

OVERVIEW OF INITIAL THERAPY RECOMMENDATIONS FOR PATIENTS NOT ELIGIBLE FOR TRANSPLANTATION

Both MPT and VMP have excellent Phase III trial support as recommended options. Further follow-up is required to assess the longer-term outcomes with both MPT and VMP. Initial data suggest that VMP can overcome the negative impact of chromosomal poor prognostic features (see above). DVT risk

TABLE 9
Frequently Used Combinations

MP	First standard combination used for initial therapy
CP	Alternative to MP
ABCM	Combination used in Europe, especially UK. Little extra benefit versus MP
VAD	Once the most commonly used alternative to MP, now increasingly replaced with more active combinations including the novel therapies
D or MD or CD	D alone or combined with M or C can be used as alternative to VAD. Avoids need for four-day infusion.
TD	(thal/dex) frontline combination, now largely replaced by Rev/dex in the US
MPT	(MP+thal) To increase efficacy of MP
MPR	(MP+Revlimid®) To increase efficacy of MP
VMP	(MP+VELCADE®) FDA approved for frontline use
VMPT	(MP+reduced-frequency VELCADE® and reduced-dose thalidomide) To increase efficacy of MP with less neuropathy
RD or Rd	(Rev/dex) Popular frontline combination (NCCN category 1) D= full-dose dex; d=low-dose dex, one day per week
BD or VD	(VELCADE®/dex) FDA approved for frontline use
RVD	(Revlimid®+VELCADE®+dex) Promising combination in late clinical trials for both newly diagnosed and relapsed myeloma
CVD ("CyborD")	(Cytosan®+VELCADE®+dex) Promising combination in trials for both newly diagnosed and relapsed myeloma

is a concern with MPT, but not with VMP. MPT is completely oral, whereas VMP incorporates the I.V. VELCADE® component. Both MPT and VMP have an associated neuropathy risk. The painful neuropathy with VMP is possibly a greater concern, although reducing the frequency of VELCADE® to once weekly may alleviate this problem.

Alternatively, the simple two-drug options MP, Thal/Dex, RevloDex, or Vel/dex can be considered depending upon the clinical situation.

IF STEM CELL HARVEST IS PLANNED

The approach to frontline or induction therapy has evolved and changed considerably over the last two decades.

VAD Chemotherapy: NCCN category 2B choice – The VAD protocol, first introduced in 1984, became a popular alternative to MP or CP induction. Significant disadvantages, including possible infection and blood clotting problems, as well as superior response rates with thalidomide/dexamethasone, Revlimid®/dexamethasone, and bortezomib with or without dexamethasone, have now made VAD a less common option worldwide.

Thalidomide/dexamethasone (Thal/Dex): NCCN category 2B choice – Thal/dex is a standard option for front-line therapy, with a response rate of 64%. Improved response rates and far lower incidence of peripheral neuropathy with RevloDex have made this newer combination a preferable option, where and when available.

VELCADE®: NCCN category 1 choice – In June 2008, VELCADE® was approved for use in the frontline setting. Although it is a very active single agent, it is expected that it will be used mostly in combination therapy, adding to the arsenal of options available to newly diagnosed patients as well as to those with refractory and/or relapsed disease. A variety of bortezomib (VELCADE®) combinations is now available:

- Bortezomib/thalidomide/dexamethasone (VTD): NCCN category 1 choice – Cavo *et al.* recently compared thalidomide/dexamethasone to VTD in a randomized controlled trial involving 256 patients. The CR plus VGPR rate after 3 courses of 21 days was significantly higher for VTD (60%) compared with thalidomide/dexamethasone (27%).
- Bortezomib/dexamethasone (NCCN category 1 choice) versus VAD – Several studies have shown initial overall response rates (ORR) of 70%-90% with bortezomib/dexamethasone (Vel/dex) as first therapy. In a recently reported trial, Harousseau *et al.* compared Vel/dex with VAD as pre-transplant induction. The CR + VGPR rates were: Vel/dex 47% versus VAD 19% pre-transplant, and Vel/dex 62% versus VAD 42% post-autologous stem cell transplant, both significant differences.
- Other bortezomib combinations – Numerous bortezomib (VELCADE®) combinations are currently being evaluated. Several have produced promising

results in Phase II-III trials including: VCD (VELCADE®/Cytoxan®/Dex, also known as CyborD) – NCCN category 2A choice; VELCADE®/Doxil® ± Dex – NCCN category 2B choice; VRD (VELCADE®/Revlimid®/Dex) – NCCN category 2B choice. A recent Mayo trial of VRD vs. VCD vs. VCRD (VELCADE®/Cytoxan®/Revlimid®/Dex) indicated that all regimens had similar efficacy, but that the four-drug combination caused more toxicity and more frequently required dose reductions. Long-term follow-up data is still being collected and assessed. Mayo anticipates conducting a trial comparing VCD and VRD.

In addition, bortezomib is part of several new drug combinations in which synergy is anticipated (*see Relapse/New Drug sections on pages 35-37*).

TABLE 10
Tests Required To Monitor Therapy Responses

Blood Tests	<ul style="list-style-type: none"> • Routine blood counts • Chemistry panel • Liver function tests • Myeloma protein measurements (<i>serum protein electrophoresis plus quantitative immunoglobulins</i>) • Serum Free Light Chain Assays (Freelite™) • Serum β2 microglobulin • C-reactive protein • Peripheral blood labeling index (LI) • Serum erythropoietin level
Urine	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Skeletal survey by X-ray • MRI/CT scan for special problems • Whole body FDG/PET scan if disease status unclear • Bone density measurement (DEXA scan) as baseline and to assess benefit of bisphosphonates
Bone Marrow	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • Amyloidosis • Neuropathy • Renal or infectious complications

Revlimid® Combinations in a Pre-Transplant Setting – The results with lenalidomide (Revlimid®)/dexamethasone have been noted already. In essence, Rev/Dex can be used for induction when there is intent to proceed with harvest and stem cell transplantation, even though that has not been the priority in trials conducted thus far. The induction results are excellent and comparable to the bortezomib combinations. Stem cell harvesting may require growth factor plus cyclophosphamide or plerixafor (Mozobil®) versus growth factor (e.g., Neupogen®) alone. Further studies are required to explore the use of Revlimid® in the pre-transplant setting.

Induction Therapy Recommendations for Transplant Candidates – The options with Phase III randomized trial support are:

- Thal/Dex (TD)
- VELCADE®/Dex (VD)
- VELCADE®/Thalidomide/Dex (VTD)
- Revlimid®/Low-Dose Dex (RevloDex - Rd)

All four regimens can produce rapid response and have high response rates. TD and Rd are exclusively oral; VTD and VD have the intravenous VELCADE® component. TD and Rd both carry an increased risk of blood clots (deep vein thrombosis, or DVT) and require aspirin or other anticoagulant treatment. Neuropathy is a concern with the thalidomide and VELCADE® regimens.

It is a challenge to select the best treatment for each patient. One must consider the early risks of treatment, responses and length of remission, 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.

2. TRANSPLANTATION

HIGH-DOSE THERAPY (HDT) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)

- The role of autologous transplantation has been extensively reviewed.
- HDT with autologous stem cell transplantation 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 approaches, 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 ≥ 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.

- The added benefit of incorporating (or not) autotransplantation is under ongoing review.
- Morbidity and mortality – 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^2 as the preparative regimen. Since the use of total body irradiation (TBI) adds toxicity without clear survival benefit, few centers recommend TBI as part of the preparative regimen.
- Both quality of life and cost-benefit analyses have been conducted for HDT compared to standard-dose chemotherapy. The Nordic Myeloma Study showed both improved quality and length of survival (median survival of 62 months versus 44) but with added expense.

Current Recommendations

HDT with autologous stem cell support should be strongly considered as part of the frontline therapy for newly diagnosed patients with symptomatic myeloma.

- a. The standard conditioning regimen is melphalan 200 mg/m^2 . Total body irradiation is not recommended.
- b. Stem cell purging is not recommended because of added expense without additional clinical benefit.
- c. Peripheral blood stem cells are recommended over bone marrow both because of ease of collection and more rapid engraftment.
- d. The pre-transplant regimens are discussed above.
- e. Several novel therapy combinations are being introduced as pre-transplant regimens.

ROLE OF AUTO TRANSPLANTATION AT TIME OF FIRST RELAPSE

Part of the decision process for autotransplant involves knowledge of the impact of waiting, with a view to transplant at relapse. Data from two French randomized trials indicate no reduction in overall survival from waiting to do the transplant at relapse. Quality of life becomes an important consideration. On the one hand, if transplant is not performed as a planned primary strategy, then typically additional therapy, including maintenance, is required, with corresponding toxicity and side effects. On the other hand, the major impact of the transplant is deferred, which for some patients is a better personal choice. Combination therapies that include the novel agents Revlimid®, thalidomide, and VELCADE® as front-line treatment are resulting in response and progression-free survival rates comparable to that of ASCT, allowing patients and their physicians the choice of postponing ASCT without sacrificing efficacy. A large, randomized US-French trial of frontline VRD vs. VRD + ASCT will help to determine if the addition of ASCT to novel therapy provides additional benefit or not.

HARVESTING AND STORING STEM CELLS FOR LATER USE

There is a strong reluctance in many 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. Nonetheless, many patients request and want their stem cells harvested, even though they may not be enthusiastic about immediate high-dose therapy.

Current Recommendations

- Harvesting with storage for future use is recommended with review on a case-by-case basis.
- There is medical and scientific rationale for saving stem cells for later use.

TABLE 11
High-dose Therapy

TYPE	ADVANTAGES	DISADVANTAGES
Single Autologous Transplant	<ul style="list-style-type: none"> 50% excellent remissions At least as good as standard therapy regarding overall survival and probably better for patients with high Sβ2M. Basis for strategies to produce true remission or long-term cure New preparative regimens may produce true complete remission 	<ul style="list-style-type: none"> Relapse pattern similar to standard chemotherapy More toxic and expensive Patients who decisively benefit from transplant not clearly identified Maintenance therapy may still be required/recommended
Double Autologous Transplant	<ul style="list-style-type: none"> 2002 update of French data indicates survival benefit for subset of patients not in CR or VGPR Excellent results with tandem transplant (<i>see text</i>) 	<ul style="list-style-type: none"> Role of double vs. single still unclear Much more toxic and expensive versus single No survival benefit if in CR or VGPR after first transplant
Traditional Allogeneic Transplant	<ul style="list-style-type: none"> No risk of contamination of marrow/stem cells with myeloma Possible graft versus myeloma effect to prolong remission 	<ul style="list-style-type: none"> Even for HLA identical siblings, significant risk of early complications and even death (25-30%) Risk of complications unpredictable Restricted to age <55 More toxic and expensive versus autologous
Mini-Allo Transplant	<ul style="list-style-type: none"> Less toxic form of allo Preparative chemotherapy usually well tolerated Results in anti-myeloma immune graft 	<ul style="list-style-type: none"> No anti-myeloma chemotherapy given Still produces graft-vs-host disease Full benefits still unclear Risk of initial mortality approximately 17%
Identical Twin Transplant	<ul style="list-style-type: none"> No risk of myeloma contamination in transplanted cells Much less risky than allogeneic transplant 	<ul style="list-style-type: none"> No graft-vs-myeloma effect Need identical twin <55

- Delayed transplant is a viable treatment option. A second transplant in a patient is a viable option, especially if a first remission of >2 years has occurred. (*See discussion below 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 certain risk factors, including older age, higher LDH, abnormal cytogenetics, or advanced disease, are not as likely to achieve extended benefit.
- Recent comparative studies, including the French randomized studies, have shown benefit predominantly for a subgroup of patients (those who are not in CR). It is possible that longer follow-up will show added benefit.

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 (Sirohi, 2001).
- 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 multiple 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 patients with myeloma.
- The potential advantages of allogeneic transplantation are myeloma-free stem cells and graft versus myeloma effect. But, despite these factors, long-term cure is rare. Relapse continues at a rate of approximately 7% per year with long-term follow-up. Graft versus host disease can also be an ongoing problem, requiring therapy and reducing quality of life.

- The graft versus myeloma effect can be enhanced by using donor lymphocyte infusions and has been clinically beneficial in some series.
- A recent cooperative group trial evaluating 710 patients randomized to non-myeloablative or “mini” allogeneic transplant vs. tandem autologous transplant was presented at ASH 2010 (Krishnan et al.). Unfortunately, this trial showed rather decisively that planned addition of mini-allo transplant as part of an upfront double-transplant approach introduced significant added risk with no survival benefit over tandem autologous transplant. Thus, routine consideration of this approach is no longer recommended.

Current Recommendations

- a. Conventional full-match allogeneic transplantation is rarely recommended as a primary strategy because the risks are too high.
- b. “Mini” allogeneic transplantation is only recommended in a clinical trial setting.
- c. 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.

3. RADIATION

Radiation therapy is an important modality of treatment for myeloma.

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 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.

Total Body Irradiation (TBI) – Total body or sequential radiation of half of the body has been used as part of an overall strategy for high-dose therapy with transplant and/or in the management of relapsing refractory disease. Although used in the past as a preparatory regimen for transplant, recent studies have shown no added benefit and, unfortunately, increased toxicity. Therefore, TBI is no longer recommended as part of preparatory regimens. In patients with refractory disease, sequential hemi-body radiation can be used to temporarily control the disease. This is rarely successful for very long, particularly in patients with aggressive, active myeloma. There is also the disadvantage that wide-field radiation destroys the normal bone marrow and makes it difficult if not impossible to use other treatment options following this approach.

4. MAINTENANCE THERAPY

Alpha Interferon – For over 15 years, many investigators have evaluated the efficacy of interferon, an agent shown to prolong remission achievable with standard or high-dose therapy. Conflicting results have been obtained, but a small benefit of 10% to 15% in the prolongation of remission and survival has been observed. Differences of 10% to 15% (i.e., 6 to 9 months) are hard to prove in clinical studies. Although some investigators think that alpha interferon may still have a definite although small role in the management of myeloma, the associated side effects can have an adverse impact on patient quality of life.

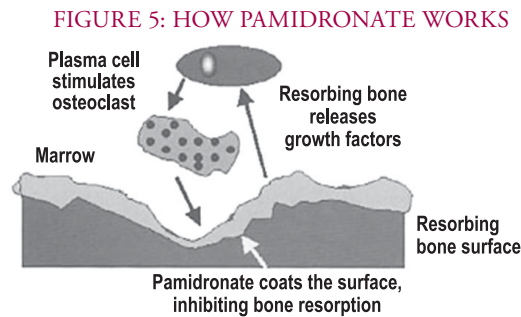
Prednisone – It has been difficult to find therapy that can prolong remissions and survival in myeloma without compromising quality of life, as is the case with alpha interferon. However, new studies have supported earlier observations from the 1980s that prednisone is an effective maintenance agent, and probably superior to alpha interferon. Prednisone administered three times per week (e.g., starting dose of 50 mg) has acceptable toxicity and can prolong both remission and survival. A particular advantage is that patients can take prednisone for several years without developing resistant myeloma cells. However, caution is required because of longer-term side effects, and dose reductions are usually necessary.

Immunomodulatory drugs (IMiDs) – Promising results are accumulating for the role of Revlimid in the maintenance setting. As reported at the 2010 annual ASH meeting, Revlimid® maintenance therapy significantly prolongs time to progression compared with placebo when given to patients with stable disease or better after high-dose melphalan/ASCT (CALGB, McCarthy *et al.*), and significantly prolongs progression-free survival when given to patients after ASCT as consolidation therapy followed by a lower dose of Revlimid® for maintenance therapy (Attal *et al.*). Follow-up data from the CALGB study indicate that Revlimid maintenance post-ASCT not only doubles progression-free survival as compared to placebo, but increases overall survival as well. Balanced against this favorable data is the low but increased risk of a second malignancy in the placebo arm of the trial. Further analysis is ongoing to determine the nature of that risk.

VELCADE® – A HOVON/GMMG phase III study comparing VELCADE®, Adriamycin®, and dexamethason (PAD) + VELCADE® maintenance, to vincristine, Adriamycin®, and dexamethasone (VAD) + thalidomide maintenance, was presented at ASH 2010. Not only did VELCADE® result in improved PFS and overall survival, but its use as maintenance therapy administered on an every-other-week schedule was well tolerated and resulted in additional responses. Initial results also indicated benefit in patients with the deletion 17p poor-risk FISH genetic feature.

5. SUPPORTIVE CARE

Erythropoietin – Erythropoietin is a naturally occurring hormone now available through genetic engineering techniques. Erythropoietin is administered to improve the hemoglobin level in patients who have persistent anemia. Erythropoietin injections (e.g., 40,000 units subq weekly) can show dramatic benefit in the level of hemoglobin and in performance status. It should be strongly considered in patients who have persistent anemia. However, under new strict guidelines, erythropoietin should only be used in the setting of ongoing active treatment for myeloma. Erythropoietin should only be continued in patients showing clear benefit. Iron supplements may be required to achieve maximum benefit. Under new FDA guidelines, it may become necessary for patients to sign informed consents to take erythropoietin. As previously noted, recombinant Epo (e.g., Epogen® or Procrit®) should be used with caution in the light of recent reports of the association of Epo with increased tumor growth and reduced survival in patients with cancer, and the identification of Epo receptors on myeloma cells, although this requires further investigation.



Bisphosphonates – 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. It is currently recommended that bisphosphonate therapy be used as an adjunctive measure in myeloma patients who have bone problems (see Figure 5). Other bisphosphonates available include clodronate (Bonfos®), an oral formulation in use in Europe for the treatment of myeloma bone disease, and zoledronic acid (Zometa®), approved in the U.S. and Europe as treatment of both hypercalcemia and bone disease. Several new bisphosphonates are in clinical trials for myeloma. One, called ibandronate (Boniva®), is now used in Europe. In the US, it is currently FDA approved only for use in postmenopausal osteoporosis.

At the 2010 annual meeting of the American Society of Hematology, a randomized comparison of zoledronic acid with clodronate as part of the MRC

Myeloma IX trial (Morgan *et al.*) showed that zoledronic acid was not only superior to clodronate in preventing skeletal-related events (SRE), but also provided a survival benefit independent of SRE reduction, supporting anti-myeloma activity of zoledronic acid.

Several concerns have emerged related to chronic bisphosphonate use. Two of these, kidney damage and a condition called osteonecrosis of the jaw (ONJ) are addressed in detail in other IMF educational materials (*Myeloma Minute*®, *Myeloma Today*®, and *Understanding Bisphosphonate Therapy*®). 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 to 45 minutes, which reduces the risk of renal impairment.

An American Academy of Oral Medicine position paper on the management of bisphosphonate-related ONJ (BONJ) was published in *The Journal of the American Dental Association* in December, 2005. The first recommendation is prevention of BONJ 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. The Mayo Clinic published the Mayo Consensus Statement for the Use of Bisphosphonates in Multiple Myeloma in August, 2006, which includes the following: “Pamidronate is favored over zoledronic acid until more data are available on the risk of complications (osteonecrosis of the jaw.)” Some modifications of these guidelines were proposed by the IMF’s International Myeloma Working Group and published in the *Mayo Clinic Proceedings* in March, 2007. At the 2009 annual meeting of the American Society of Hematology, key opinion leaders noted that the incidence of ONJ appears to have decreased dramatically, probably due to improved dental hygiene.

However, additional concerns have emerged with long-term use of bisphosphonates. Atypical (subtrochanteric) fractures of the femur are rare, and there is data that establishes an association with five or more years of bisphosphonate treatment with their occurrence. In October, 2010, the FDA added subtrochanteric fracture of the femur to the “Precautions and Warnings” section of the package inserts for all bisphosphonates. Two recent publications discuss the possible association between oral bisphosphonates and cancer of the esophagus. Using the same database, one group did not find an association (Cardwell *et al.*), whereas the other group reported an increased risk (Green *et al.*). These findings require further examination.

The International Myeloma Working Group (IMWG) recommends discontinuing bisphosphonates after one year of therapy for patients who achieve complete response and/or plateau phase. 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. Current guidelines on the role of bisphosphonates in multiple myeloma from the American Society of Clinical Oncology (ASCO) (Kyle *et al.*, *J Clin Oncology* 2007) recommend treating for two years, then considering discontinuation of bisphosphonates for patients whose disease is responsive or stable. Continued use of bisphosphonates should be at the discretion of the physician.

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 preventative or prophylactic antibiotics with recurrent infection is controversial. A recent comparative study (URCC/ECOG, 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 2 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. The use of high-dose gamma globulin may be required in patients with acute and severe recurrent infections. GM-CSF may be helpful to improve the white blood cell levels in an effort to overcome infectious complications. The use of G- or GM-CSF is helpful in the recovery phase following bone marrow or stem cell transplantation. G- and GM-CSF are also used in harvesting stem cells.

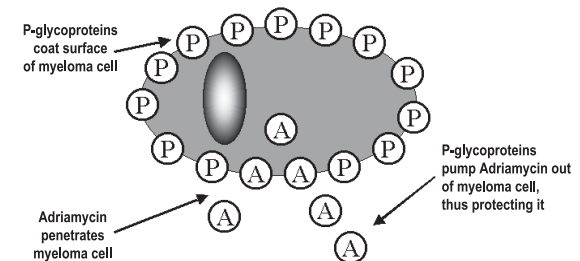
Antivirals – An increased incidence of herpes zoster (shingles) has been observed in some patient populations with myeloma (but not other malignancies) who are treated with VELCADE®. Therefore, prophylactic antiviral therapy should be considered with VELCADE® therapy. This has led to the recommendation that patients on clinical trials of carfilzomib, a second-generation proteasome inhibitor, receive antiviral prophylaxis. Myeloma patients are cautioned not to get the shingles (Zostavax®) vaccine, as it is a live virus that poses a significant risk to those who are immune compromised.

6. MANAGEMENT OF RELAPSING OR REFRACTORY DISEASE

As illustrated in the pathophysiology section, a frequent problem in myeloma is the relapse that occurs following a 1- to 3-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.

If first relapse occurs after a remission of at least 6 months to 1 year, the first strategy is to consider re-utilizing the therapy that produced the remission in the first place. 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 over one year following the initial induction attempt. As an example, a patient who has received MP and whose myeloma has gone into remission for two years can again receive MP induction. If remission has lasted less than six months, some alternative therapy will usually be required. This is also the case if relapse has occurred following a second or third use of the original induction therapy. The use of an Adriamycin®- or Doxil®-containing regimen is an important consideration in this setting. (See Figure 6, the multi-drug-resistant [MDR] myeloma cell.)

FIGURE 6: MDR MYELOMA CELL



VELCADE® (bortezomib) for relapsing myeloma – The availability of VELCADE® for relapse treatment has been a major step forward. After its approval for patients with multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy, VELCADE® was then evaluated in a multicenter phase III “APEX” randomized trial comparing VELCADE® to high-dose dexamethasone in 669 myeloma patients at 80 sites who had relapsed following one to three prior lines of therapy. The primary end point was time to progression. APEX also assessed the role of VELCADE® as maintenance therapy in responders. This study recruited internationally and was the largest study ever completed in multiple myeloma. Overall, there was an approximately 30% improvement in survival during the first year with bortezomib (VELCADE®) as opposed to dexamethasone. This was obviously very helpful information, and led to VELCADE®’s role as a platform on which to base combination therapies for relapse (Vel/Doxil®, VR, VRD, VCD, etc.).

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. Whether a second high-dose therapy with transplant is the most appropriate strategy as opposed to some other lower-dose chemotherapy approach is currently unclear, and must be based upon individual patient considerations.

Given the continuing rapid rate of development of new therapies for myeloma, including second-generation proteasome inhibitors, third-generation immunomodulatory drugs, monoclonal antibodies, and targeted therapies, 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.

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, 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 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 area, reducing movement and pain. Moderate exercise is also important in recovering bone strength and mobility and can help in overall pain reduction.

7. NEW AND EMERGING TREATMENTS

Most new treatments are available in the setting of clinical trials. Clinical trial phases are listed in Table 11. A whole range of agents is currently in

TABLE 12
Clinical Trial Phases

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

clinical trials, including proteasome inhibitors and immunomodulatory agents, monoclonal antibodies, histone deacetylase (HDAC) inhibitors, heat shock protein (HSP) inhibitors, chemotherapeutic agents, and therapies targeted to myeloma-specific pathways. Patients are encouraged to contact the IMF via telephone (800-452-CURE [2873] in the U.S. and Canada, +1-818-487-7455 elsewhere) or Internet (myeloma.org) and to check with their physicians regarding the availability of new clinical trials. The *Myeloma Matrix*[®], an IMF publication that lists all drugs currently in clinical trials for myeloma, is available with regular updates in print and with on-going updates on the IMF web site. Very good summaries of new therapies are presented in the IMF reports from ASH, ASCO, EHA, and IMWG (all available by calling the IMF or on line at myeloma.org).

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NOTE: References rather than formal footnotes are provided as background source material for each major section of the booklet. Within sections, articles are listed alphabetically by author.

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