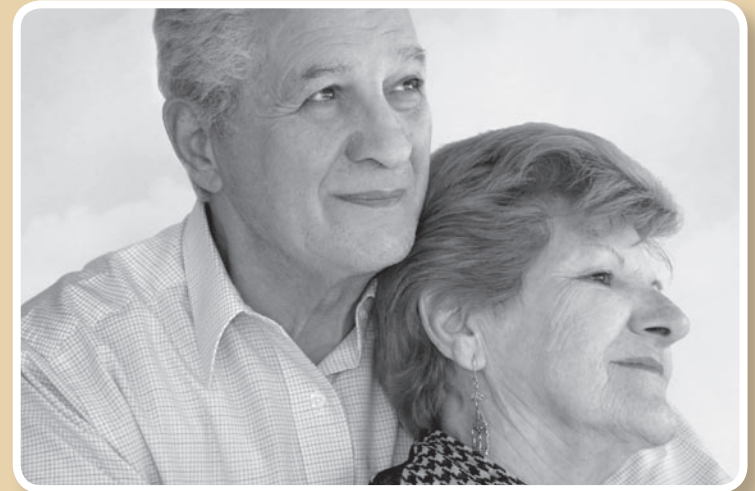


# Concise Review

of the Disease and Treatment Options



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*Dedicated to improving the quality of life  
of myeloma patients while working  
towards prevention and a cure.*

## Multiple Myeloma

Cancer of the Bone Marrow



International Myeloma Foundation

2006 Edition

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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.

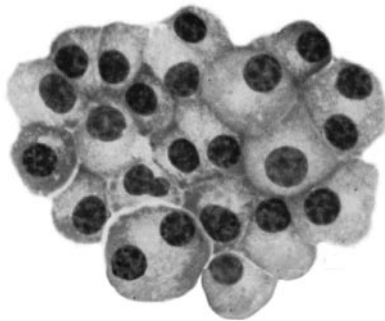
## WHAT IS MYELOMA?

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 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

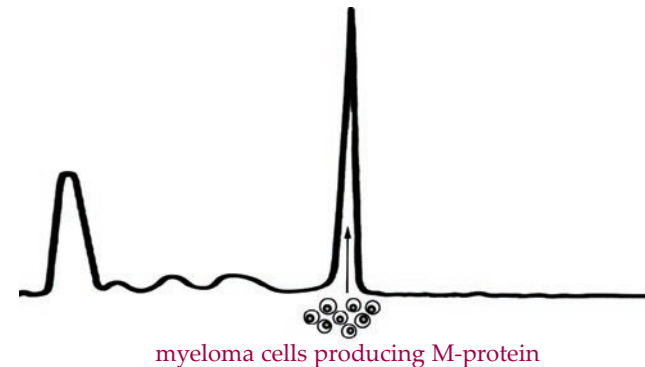
FIGURE 1: PLASMA (MYELOMA) CELLS



## 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, myeloma protein, para-protein, or the protein spike. The monoclonal protein is called a spike because of the way it appears on protein electrophoresis, a laboratory technique to separate and identify proteins (see Figure 2).

FIGURE 2: MONOCLONAL SPIKE

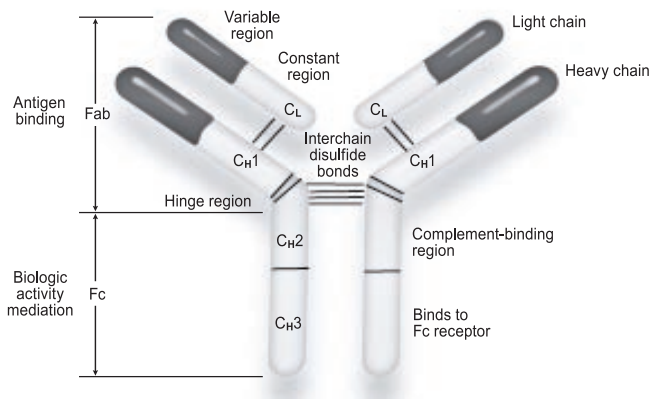


The monoclonal protein is an immunoglobulin or a component/fragment of an immunoglobulin. Figure 3 illustrates the structure of a normal immunoglobulin molecule. In myeloma cells, one or more mutations have occurred in the genes responsible for immunoglobulin production. Myeloma proteins therefore have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

This abnormal immunoglobulin structure and function has a number of consequences:

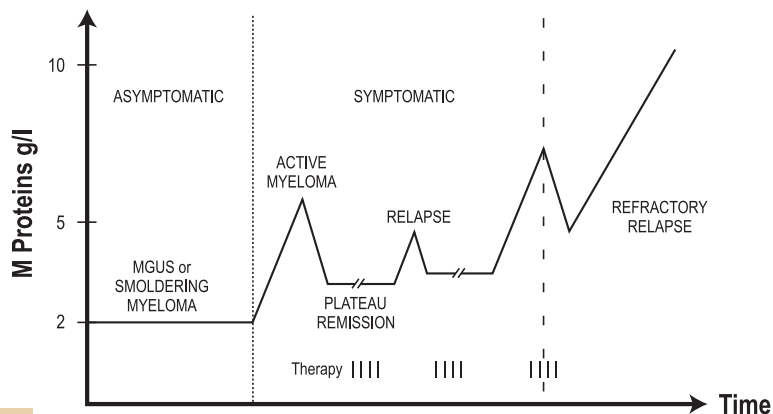
- The excess M-protein accumulates in the blood stream and/or is excreted in the urine as a monoclonal spike.

FIGURE 3: IMMUNOGLOBULIN MOLECULE STRUCTURE



- **The abnormal monoclonal molecules can adhere** to each other and/or other tissues such as blood cells, blood vessel walls, and other 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 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 or enhanced blood clotting or phlebitis
  - Binding to circulating hormones or chemicals, resulting in a variety of endocrine or metabolic dysfunctions.

FIGURE 4: DISEASE PHASES



- **Free Bence Jones proteins can also adhere** to each other and/or to other tissue (just as the whole immunoglobulin can). In this case the end result is either:

1. Amyloidosis – A disease entity in which the Bence Jones light chains cross link in a highly symmetric  $\beta$ -pleated fashion and become deposited in tissue around the body, including, for example, kidney, nerves, and heart-tissue; or
2. Light Chain Deposition Disease – The light chains are deposited in a more haphazard fashion, but most especially in small blood vessels of the eyes and kidneys.

Even in the absence of bodily dysfunction, routine blood testing may give very strange results because of “stickiness” or hyperviscosity of myeloma blood samples in automated chemical analyzers and/or interference with chemical reactions necessary for routine testing.

## ANNOTATED HISTORY

*Dr. Henry Bence Jones was the first to investigate a strange protein in the urine of a myeloma patient. What caught Dr. Bence Jones' attention was a urine protein that dissolved on boiling, but re-precipitated on cooling: what proved to be “Bence Jones” light chains. It turned out that the patient also had a very strange bone disease which 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 “mollities and fragilitas ossium” (soft and fragile bones). The first patient, Thomas Alexander McBean, was diagnosed in 1845 by Dr. William Macintyre, a Harley Street consultant 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, noted and published 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. It has been noted that 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) shows up on X-rays.

- 1909 Weber suggested that plasma cells in the bone marrow actually produce 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 was introduced to allow 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 gammaglobulin as well as abnormal serum proteins. In their honor, the two types of Bence Jones proteins are called Kappa (K), and Lambda (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, by Alexanian, was shown to give 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. This 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  $\beta 2$  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 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. Herpes virus (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™ and Actimid™), long-acting Adriamycin analogues (e.g. Doxil®), arsenic trioxide (Trisenox®), anti-angiogenesis agents (e.g. VEGF tyrosine kinase inhibitor), agents to block cell adhesion, betathine, and proteasome inhibitors (e.g. VELCADE®).
- 2001
- New classification system proposed for myeloma and related diseases (see Table 1 below).
  - New prognostic factor or staging systems proposed:

- 2001 con't
- SWOG (Southwest Oncology Group) uses separation into 4 groups based upon serum  $\beta$ 2 microglobulin and serum albumin.
  - IFM (French Study Group) uses separation into 3 groups based upon serum  $\beta$ 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. Overall benefit noted, especially for patients with high serum  $\beta$ 2 microglobulin (> 7.5 mg/dl).
- 2003
- VELCADE® (bortezomib; formerly PS-341) approved by the F.D.A. as treatment for actively relapsing myeloma following at least 2 prior therapies.
  - MRC autotransplant results provided the second randomized dataset 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. However, no apparent added benefit for patients already in complete remission with the first transplant. Other questions about the overall role of double transplant persist.
  - Little Rock group (Shaughnessy/Barlogie) show 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 were presented indicating a 59% response rate with the combination versus 41% with dexamethasone alone (ECOG Criteria).
  - Results of multi-institutional randomized trial comparing VELCADE® with dexamethasone were presented showing superiority for VELCADE® (details discussed in text).
  - Early results with VELCADE® in the frontline setting presented showing 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. Further follow-up is required.
  - New myeloma staging system, the I.S.S. (International Staging System), introduced. See page 15.
- 2005
- Two large Phase III trials showed that Revlimid® (lenalidomide) plus dexamethasone is superior to dexamethasone alone in relapsed myeloma (time to progression > 15 months v. 5 months). FDA approval is anticipated in 2006.

- 2005 con't
- International Staging System (ISS) developed by the International Myeloma Working Group of the International Myeloma Foundation (IMF) is published (see page 15). New response criteria for assessing treatment benefit is also developed and is scheduled for publication in early 2006.
  - Numerous new agents in early development. Heat shock protein-90 inhibitors enter Phase I – II trials.
  - Addition of thalidomide to standard melphalan/prednisone regimen shows remarkable added benefit. Several upfront trials are ongoing.

## EPIDEMIOLOGY

The average incidence of myeloma is 3-4/100,000 in the US, representing approximately 1% of all types of cancer. There are approximately 15,000 new cases of myeloma in the US each year. Myeloma is more common in African Americans than Caucasians. For example, in Los Angeles County the incidence of myeloma in African American men is 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 3:2. 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.

## 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 for myeloma patients is illustrated in Figure 4. It is important to note that there are frequently multiple periods of response and remission. The patho-physiology of myeloma is summarized in Table 2 in schematic form

## BONE DISEASE

TABLE 1

**DEFINITIONS OF MYELOMA AND RELATED MONOCLONAL GAMMOPATHIES**

STANDARD NAME	PROPOSED NEW NAME	DEFINITION
MGUS (Monoclonal Gammopathy of Underdetermined Significance)	MGUS (i.e., NO CHANGE)	<ul style="list-style-type: none"> <li>• Monoclonal protein present</li> <li>• No underlying disease state</li> </ul>
SMOLDERING or INDOLENT MYELOMA	ASYMPTOMATIC MYELOMA	<ul style="list-style-type: none"> <li>• Higher level of disease than MGUS, but still no symptoms or organ damage</li> </ul>
MYELOMA	SYMPTOMATIC MYELOMA	<ul style="list-style-type: none"> <li>• Monoclonal protein present, and</li> <li>• One or more “CRAB” features of organ damage present*</li> </ul>

\*Organ damage classified as “CRAB”

C - calcium elevation (> 10 mg/l)

R - renal dysfunction (creatinine > 2 mg/dl)

A - anemia (hemoglobin < 10 g/dl)

B - bone disease (lytic lesions or osteoporosis)

ONE OR MORE required for diagnosis of SYMPTOMATIC MYELOMA

Ever since the first recognition of myeloma in 1844, the presence of abnormal protein has been linked with bone destruction. 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 characterization of local cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  and - $\beta$ ; chemokines such as MIP-1 $\alpha$ ; and cell-cell adhesion processes involving av  $\beta$ 3 integrin, all of which are involved in producing increased numbers and activity of osteoclasts. Most recently a substance called RANK ligand (RANKL) has been identified as a critical mediator of osteoclast activation. Studies are already underway to evaluate the clinical efficacy of specific inhibitors of RANKL, namely RANK.Fc and osteoprotegerin (OPG), both of which have shown promise in laboratory studies and preliminary clinical testing. A completely new finding is the observation by the Little Rock group that lytic bone disease is associated with local production of a protein called DKK-1. This is yet another angle for new therapeutic strategies.

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 under investigation. An important new observation is that the cholesterol-lowering drugs, statins (i.e. Lipitor<sup>®</sup>, Mevacor<sup>®</sup>, Baycol<sup>®</sup>, etc.), can enhance osteoblast activity and promote bone healing. In addition, the new agent VELCADE<sup>®</sup> (see relapse treatment) has been shown to promote bone healing, in addition to being a potent anti-myeloma agent. Studies to further investigate the benefit of such drugs in myeloma are under way.

## ANEMIA

Anemia is a characteristic feature of myeloma. Although simple physical displacement of marrow red 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. TNF- $\alpha$  has been identified as one important inhibitor of erythropoiesis; active myeloma, however, results in a complex interplay of factors that can cause not just anemia, but neutropenia, and strangely, sometimes either increased or decreased platelet counts. Interleukin-6 is the factor most responsible for increased platelet counts levels. Increases in basophils, eosinophils, and monocytes can also occur. Improvement in anemia occurs with successful treatment for the myeloma and can be enhanced by use of recombinant erythropoietin (Epogen<sup>®</sup>, Procrit<sup>®</sup>, or Aranesp<sup>®</sup> (darbapoietin)).

## KIDNEY DYSFUNCTION

Impairment of kidney function is a common complication in myeloma patients. 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, or 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, or contrast/dyes used for diagnostic studies. Awareness of potential kidney damage and maintaining excellent fluid intake are especially important for myeloma patients to help avert the damaging effects of these various factors.

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)

**EXTRA SKELETAL 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, light chains)
- Narrowed anion gap (low serum sodium)
- Elevated serum  $\beta$ 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

**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. Because of the susceptibility to infection, viral infections of nerve tissue are quite common, most particularly varicella zoster (shingles) and Bell's palsy (partial facial paralysis).
- **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 functions, including 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 functions.

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 catheter), the whole range of bacterial, fungal, and opportunistic infections occurs in myeloma patients undergoing therapy.

## TYPES OF MYELOMA

The type of monoclonal protein produced varies from patient to patient. The most common is IgG and the rarest 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 myeloma patients 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.

TABLE 3  
TYPES OF MONOCLONAL PROTEIN (%)

1. Serum	%	Totals
IgG	52	75%
IgA	21	
IgD	2	
IgE	<0.01	
2. Urine (Bence Jones or light chains only) types $\kappa$ and $\lambda$		11%
3. Two or more monoclonal paraproteins	<1%	2%
Heavy chains (G or A) only	<1%	
No monoclonal paraprotein	1%	
4. IgM (rarely myeloma typically associated with Waldenström's Macroglobulemia)		12%
<b>TOTAL</b>		<b>100%</b>

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

Hypercalcemia, traditionally present in 30% of the 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. Hyperviscosity, due to high myeloma protein levels, can cause problems such as bruising, nose bleeding, hazy vision, headaches, gastrointestinal bleeding, sleepiness, and a variety of ischaemic neurological symptoms caused by reduced blood and oxygen supply to the nerve tissue. Hyperviscosity occurs in <10% of myeloma patients. Hyperviscosity affects about 50% of patients with Waldenström's Macroglobulinemia (IgM paraprotein or M-component). Increased bleeding is often accentuated by thrombocytopenia, in addition to the binding of monoclonal proteins to clotting factors and/or platelets.

Neurologic involvement can result in specific problems depending on location. 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  $\beta$ -pleated form).

## STAGING AND PROGNOSTIC FACTORS

Prognosis in myeloma is determined by both the number and specific properties of myeloma cells in a given patient. These specific properties include the growth rate of myeloma cells, the production rate of monoclonal proteins, and the production or nonproduction 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. However, numerous groups have proposed new systems to more accurately and simply stage and/or classify myeloma patients into prognostic categories. Thus far, no new system has gained universal acceptance.

Just recently, however, a new staging system has been developed by the IMF-sponsored International Myeloma Working Group. 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  $\beta$ 2 microglobulin (S  $\beta$ 2M), serum albumin, platelet count, serum creatinine, and age emerged as powerful predictors of survival and were then further analyzed.

TABLE 4  
DURIE AND SALMON STAGING SYSTEM

Criteria	Measured myeloma cell mass (myeloma cells in billions/m <sup>2</sup> )*
STAGE I (LOW CELL MASS) All of the following: <ul style="list-style-type: none"> <li>• Hemoglobin value &lt; 10 g/dl</li> <li>• Serum calcium value normal or &lt; 10.5 mg/dl</li> <li>• Bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only</li> <li>• Low M-component production rates IgG value &lt; 5.0 g/dl IgA value &lt; 3.0 g/dl Urine light chain M-component on electrophoresis &lt; 4 g/24h</li> </ul>	600 BILLION*
STAGE II (INTERMEDIATE CELL MASS) Fitting neither stage I nor stage III	600 TO 1,200 BILLION*
STAGE III (HIGH CELL MASS) One or more of the following: <ul style="list-style-type: none"> <li>• Hemoglobin value &lt; 8.5 g/dl</li> <li>• Serum calcium value normal or &gt; 12 mg/dl</li> <li>• Advanced lytic bone lesions (scale 3)</li> <li>• High M-component production rates IgG value &gt;7.0 g/dl IgA value &gt; 5.0 g/dl Urine light chain M-component on electrophoresis &gt; 12 g/24h</li> </ul>	> 1,200 BILLION*
SUBCLASSIFICATION (EITHER A OR B) <ul style="list-style-type: none"> <li>• A: relatively normal renal function (serum creatinine value) &lt; 2.0 mg/dl</li> <li>• B: abnormal renal function (serum creatinine value) &gt; 2.0 mg/dl</li> </ul>	
<i>Examples: Stage IA (low cell mass with normal renal function)            Stage IIIB (high cell mass with abnormal renal function)</i>	

\*myeloma cells in the whole body

TABLE 5  
INTERNATIONAL STAGING SYSTEM (ISS)

STAGE	CRITERIA
1	Serum $\beta$ 2 microglobulin <3.5 mg/dl Serum albumin $\geq$ 3.5 g/dl
2	Not 1 or 3*
3	Serum $\beta$ 2 microglobulin >5.5 mg/dl

\*There are 2 possibilities for stage 2:

- Serum  $\beta$ 2 microglobulin < 3.5 mg/dl, but serum albumin < 3.5 g/dl  
or
- Serum  $\beta$ 2 microglobulin 3.5 – 5.5 mg/dl irrespective of the serum albumin

A combination of serum  $\beta$ 2 microglobulin and serum albumin provided the simplest, most powerful and reproducible three-stage classification. This new 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; patients < and > 65 years of age; with standard therapy or autotransplant; and in comparison with the Durie/Salmon system. The ISS is simple, based upon easy to use variables (serum  $\beta$ 2M and serum albumin), and has been introduced for widespread use.

Other more sophisticated prognostic factors are still being further evaluated. For example, chromosome 13 abnormalities determined by cytogenetic and/or FISH (Fluorescent In Situ Hybridization) analysis, although known to impact prognosis, do not add to the predictive power of the ISS approach. Nonetheless, it is hoped that classification and staging at the molecular level will emerge soon as a systematic basis for selection of new targeted treatment strategies.

## DEFINITION OF CLINICAL RESPONSE

There are several methods to classify response to treatment (see Table 7). Many variations of this classification are in use. Improvements in M-component must be associated with evidence of clinical improvement (reduced bone pain, improved anemia, etc.). With the possible exception of complete response, it is important to keep in mind that a higher percent regression does not necessarily confer a better survival. When there is residual disease, the characteristics of the remaining drug-resistant myeloma cells determine the outcome. The fraction of resistant myeloma cells is primarily dependent upon the pre-treatment tumor burden or stage. Responding patients go from a high-risk to a lower-risk status until,

ideally, no signs of MM are left, or they achieve a stable plateau phase, but with measurable residual disease. The time required to achieve the plateau phase is variable, ranging from 3-6 months (rapid response), to 12-18 months (slow response). Please refer to Figure 4 on page 3.

## 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 stem cell transplant (PSCT). In the standard type of BMT or PSCT, 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). There is as yet no consensus as to the best way to manage myeloma. However, the following will provide some guidelines.

### EXCLUDE MGUS OR ASYMPTOMATIC MYELOMA

The first and most important decision is to ascertain if therapy is required. Patients with MGUS and asymptomatic myeloma 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, research options such as anti-idiotypic vaccines are available. Bisphosphonate therapy can be used for patients with early bone disease. Erythropoietin can be considered for treatment of isolated anemia.

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 (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 myeloma protein. 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 appear in Table 8.

## 1. STANDARD-DOSE CHEMOTHERAPY:

### INTRODUCTION

The first type of treatment for myeloma appeared when melphalan was first 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.
- There are oral alternatives to melphalan/prednisone such as thalidomide and dexamethasone which do not damage stem cells. Also, Cytoxan rather than melphalan is an option. Thus simple oral therapy can be used safely without a firm prospective decision about stem cell approaches.

TABLE 6

### MYELOMA TREATMENT OPTIONS

1. Chemotherapy
2. High dose-therapy with transplant
3. Radiation
4. Maintenance therapy (e.g. alpha interferon, prednisone)
5. Supportive care:
  - Erythropoietin
  - Bisphosphonates
  - Antibiotics
  - Exercise
  - Emergency care (e.g. dialysis, plasmapheresis, surgery)
  - Pain medication
  - Growth factors
  - Brace/corset
6. Management of drug-resistant or refractory disease
7. New and emerging treatments:
  - Thalidomide and analogs Revlimid®/Actimid®
  - VELCADE® (proteasome inhibitor)
  - Doxil® (long-acting adriamycin) to substitute for adriamycin infusion
  - Trisenox® (arsenic trioxide) in clinical trials
  - Mini-allo (non-myeloablative) transplant
  - Heat shock protein -90 inhibitors

## CURRENT STANDARD-DOSE CHEMOTHERAPY RECOMMENDATIONS IF STEM CELL HARVEST IS NOT A PLANNED OPTION

This choice can relate to age, general medical condition, personal choice, or other factors.

**Melphalan/Prednisone (MP)** – The MP combination is still widely used for the treatment of elderly patients. However, even in this population, as discussed below “New Options”, thalidomide plus dexamethasone is often used or thalidomide is added to the MP regimen to achieve greater efficacy. With the MP regimen alone, 60% of patients have at least a partial response, reflected by a 50% improvement in the M-protein level plus improvement in blood count and other blood test results, along with improvement in the various symptoms of the disease, such as bone pain and fatigue. Cytoxan can be substituted for melphalan (CP) since it has similar anti-myeloma activity. Cytoxan is less toxic to normal bone mar-

**TABLE 7**  
**RESPONSE CATEGORIES**

TYPE	DEFINITION
COMPLETE RESPONSE (CR)	<ul style="list-style-type: none"> <li>• M-Protein* no longer detectable in blood and/or urine</li> <li>• Bone marrow shows no evidence of myeloma</li> <li>• Other tests confirm remission status</li> </ul>
NEAR COMPLETE RESPONSE (NCR)	<ul style="list-style-type: none"> <li>• M-Protein* is no longer measurable but can still be found with sensitive testing</li> <li>• Bone marrow shows evidence of residual myeloma but &lt; 5%</li> </ul>
PARTIAL RESPONSE (PR)	<ul style="list-style-type: none"> <li>• M-Protein* reduced by &gt; 50% but still a measurable amount remains</li> <li>• Bone marrow plasma cells reduced by &gt; 50% but still &gt; 5% remain</li> </ul>
MINIMAL RESPONSE (MR)	<ul style="list-style-type: none"> <li>• M-Protein* reduced by &gt; 25% but &lt; 50%</li> </ul>
STABLE DISEASE (SD)	<ul style="list-style-type: none"> <li>• M-Protein* changes by &gt; ±25%</li> </ul>
PROGRESSIVE DISEASE (PD)	<ul style="list-style-type: none"> <li>• M-Protein* increases by &gt; 25%</li> </ul>

\* M-Protein is the level of the monoclonal protein measured by protein electrophoresis in serum (SPEP) or 24 hr. urine (UPEP).

\*\* Changes in M-Protein must be supported with other evidence of treatment benefit to confirm response.

\*\*\* Some groups use a subcategory of “very good partial response” (VGPR) to indicate response close to complete response

row stem cells and can be considered in patients who want to remain candidates for future stem cell transplantation. It has more immediate side effects than melphalan, including such Gastro-intestinal toxicity as nausea.

**More Complex Combination Schedules** – Since the mid-1960s, many combinations and permutations of the most commonly used drugs have been tried (see Tables 8 and 9). Combinations for which there is a suggestion of additional benefit versus MP or CP are identified. The M2 protocol was developed at Memorial Sloan-Kettering Cancer Center in New York. A few studies have suggested that there is a higher response rate and an overall better outcome using the M2 protocol versus MP. For example, in a recent analysis from the Eastern Cooperative Oncology Group (ECOG), the overall survival of patients treated with M2 proved to be identical to those receiving MP; the survival at five years, however, was superior in the M2 protocol arm. The toxicity and the costs are significantly greater with the M2 combination strategy. Similar information has been gathered with the VMCP/VBAP and ABCM protocols. These have shown some indications of superiority versus MP, but they are more toxic and expensive. Proponents of these combination schedules, those who have used them for many years, continue to recommend them because the outcome is at least as good as with MP and there is a suggestion that it may even be slightly better. The current trend is to use MP or CP as a first choice and reserve the more complex combinations as a back-up approach for patients who fail to have a satisfactory response.

**New Options** – The most significant new option in this setting is the combination of MP plus thalidomide as a first therapy. In essence, this consists of adding thalidomide 100 mg by mouth daily. The group from Torino, Italy has reported excellent results, including improvement in the overall response rate to 94%, with about half of these being complete responses. Some increased risk of infection, blood clotting problems (deep vein thrombosis), and peripheral neuropathy are concerns; but preventative measures with antibiotics, anticoagulants, and anti-neuropathy strategies can help avert these problems. A trial has directly compared MP with MP plus thalidomide, and shown added benefit for the three drug combination.

## IF STEM CELL HARVEST IS PLANNED

**VAD Chemotherapy** – The VAD protocol, first introduced in 1984, became a popular alternative to MP or CP induction. The major reason for this was that it can produce response without injuring the normal bone marrow stem cells. However, significant disadvantages have emerged, including possible infection and blood clotting problems. In addition, high-dose dexamethasone, which is part of VAD, can be very helpful in patients with initial aggressive disease and/or renal failure who need rapid disease control to improve urgent medical problems. A simple alternative when faced with these types of problems is to use

TABLE 8  
**Most Commonly Used Chemotherapy Drugs**

DRUG NAME	OTHER TREATMENT NAME	COMMENTS
Melphalan* (M)**	Alkeran® (by mouth or IV)	Best single agent for treatment
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
BCNU* (B)**	Bis-chloro-Nitrosurea® (IV only)	Similar to M and C but less effective and more toxic especially bone marrow and lung toxicity
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 only)	Modest activity, frequently used as part of combination regimens (e.g. VAD)
Doxorubicin (A)**	Adriamycin® (IV only)	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 as part of combinations (e.g. EDAP and DT-PACE).

\* Alkylating agents

\*\* Common abbreviations

dexamethasone alone. This can dramatically improve the clinical situation without reducing blood count levels and without the need for insertion of an intravenous catheter followed by a four-day infusion.

**Thalidomide/dexamethasone (Thal/Dex)** – Owing to the success of Thal/Dex in the relapse setting, several groups have introduced thalidomide in a frontline setting. A Mayo Clinic study combining pulse dexamethasone with thalidomide produced a response rate of 64%. A subsequent randomized phase III trial of thalidomide plus dexamethasone versus dexamethasone alone from ECOG produced a 68% response for Thal/Dex versus 46% for dexamethasone alone. Since the 68% result is very similar to that achievable with VAD, and because of the disadvantages of VAD noted above, the thalidomide/dexamethasone combination has rapidly emerged as a leading frontline option. Many studies are ongoing. No large trial data sets are available. Several issues are unresolved, including thalidomide dose, dexamethasone dose and schedule, and concomitant supportive care/treatment/medications, such as prophylactic anticoagulation. Currently, 200 mg of thalidomide a day is recommended, although lower doses such as 50-100 mg can be equally effective and less toxic. Thus thalidomide/ dexamethasone can be strongly considered as a frontline treatment option. Since the Mayo Clinic and ECOG studies both incorporated stem cell harvesting and subsequent HDT, this is a reasonable treatment setting for prior thalidomide/dexamethasone. Outside of clinical trials, thalidomide is only available through the STEPS (Celgene) program or a similar monitoring procedure depending on the country and source(s) of drug (e.g. Pharmion: UK/Europe).

**New Options** – Several exciting new options have emerged. At the American Society of Clinical Oncology meeting in June 2004, VELCADE® was evaluated as part of two phase II trials. Results with both bortezomib (VELCADE®) alone (dexamethasone given after first 2 cycles) and bortezomib combined with Adriamycin and dexamethasone (the “PAD” regimen [P=PS-341 or (VELCADE®)]) were presented. Both of these early trials show remarkable benefit. Dr. Sundar Jagannath from St. Vincent’s, New York (Abstract #6551), representing the Salick Research Network, showed a 79% response rate (CR plus PR: i.e., all patients with >50% reduction in myeloma protein level) with VELCADE® plus dexamethasone in the frontline setting. Dr. Jamie Cavanagh from St. Bartholomew’s Hospital, London (Abstract #6550), reported a remarkable 94% CR plus PR rate with the three-drug PAD regimen after 4 cycles of therapy. Stem cell harvesting and transplantation has been feasible in the usual fashion in both of these trials, as was the case in the thalidomide/dexamethasone studies above.

The preliminary VELCADE® results combined with the more mature thalidomide data raises the expectation of very high response rates in the upfront setting. Considering the possible combination or sequential therapies and other strategies, the new goal becomes one of trying to achieve response for all patients as a basis for stem cell harvesting and transplant.

It is suddenly reasonable to think that this can be achieved soon.

With these high response rates, the issues and priorities become:

- What are the side effects?
- Is stem cell transplant planned?
- How quickly is response achieved?
- Is stem cell harvesting compromised?
- Which approach gives the longest response duration (remission) and long-term survival?

We are just starting to form ideas about these and other questions. Interestingly, DVT, which is a concern (16% likelihood) with thalidomide/dexamethasone, has not occurred with the frontline VELCADE® trials (0%). In the thalidomide/mephalan/prednisone study, the DVT percentage was 19%. Neuropathy of different types is an issue with all these new protocols. Of note, the neuropathy that occurred in the upfront VELCADE® trials appears to be partially or completely reversible. Further studies and follow-up are required. Stem cell transplant is feasible, except after thalidomide/melphalan/prednisone. Response is achievable rather quickly with both the thalidomide and VELCADE® combinations. Within

2 or 3 cycles of therapy, most of the achievable response has occurred. This abbreviates the up-front induction period versus VAD, for example. The major outstanding questions relate to response duration and survival with and without stem cell consolidation. These questions are now the basis for several planned trials.

This is obviously very good news. The June 2004 ASCO meeting included additional abstracts that further extend these notions. Firstly, two abstracts focused on the role of Doxil® (Abstracts #6548 and 6509). In one abstract (Abstract # 6458) presented by Mohammad Hussein from the Cleveland Clinic, the combination of Doxil® plus vincristine and dexamethasone was shown to be equally effective versus traditional VAD and much less expensive: about half the cost. In a related abstract (Abstract #6709), Dr. Antonio Vendette and colleagues evaluated the cost of 4 days of pulse Adriamycin versus the traditional 4-day VAD infusion approach. The 4-day bolus approach was < 30% of the cost, with apparent equivalent efficacy. This may prove to have relevance related to the “PAD” protocol discussed above.

In the second Doxil® abstract (Abstract #6509), Dr. Robert Rifkin, on behalf of U.S. Oncology, again showed that the Doxil® combination was equivalent in efficacy to VAD, but had several clinical advantages, including less neutropenia, alopecia, and hospital/clinic visits. In view of recent observations that Doxil® is highly synergistic with VELCADE®, there is considerable interest in Doxil® as part of frontline strategies, in a fashion comparable to PAD discussed above.

Numerous presentations at ASH 2004, the International Myeloma Workshop in Sydney, Australia in 2005 (see the IMF Sydney Guide, available thorough the IMF), ASCO 2005, as well as EHA 2005 in Stockholm, Sweden extended the observations concerning the introduction of novel therapies in both the frontline and relapse settings. It is now important for patients to discuss the latest information about the novel agents VELCADE®, REVLIMID®, and thalidomide as they might apply to their own treatment situation. Several trials in the frontline setting are ongoing.

Monitoring of Response – The most important aspect is to know if the symptoms at presentation have improved. One must assess blood count levels, chemistry results, and particularly levels of myeloma protein in the serum and urine. Important markers of myeloma activity are the serum  $\beta_2$  microglobulin, the C-reactive protein, and the labeling index in the peripheral blood and/or bone marrow. It is important to have a periodic 24-hour urine test to exclude the possibility of Bence Jones escape. This is a situation in which the urine protein may increase, even though the serum protein level has improved. Follow-up X-rays of the bones are important to exclude possible new bone involvement. Additional scanning, including MRI and CT, may be necessary to more closely evaluate the status of the bones. DEXA scan can be used to quantify base-line and follow-up bone density.

TABLE 9

**FREQUENTLY USED COMBINATIONS**

MP	Standard combination for initial therapy
CP	Alternative to MP
VBMCP (M2)	Combination often used in eastern USA. Proponents suggest better response and survival versus MP
VMCP/VBAP	Combination developed by SWOG and often used in western USA. More toxic with minimal increased benefit as is true for M2
ABCM	Combination used in Europe, especially UK. Little extra benefit versus MP
VAD	Most commonly used alternative to MP, especially if: <ul style="list-style-type: none"> <li>• Myeloma is aggressive</li> <li>• There is renal insufficiency</li> <li>• High dose therapy with transplant is planned</li> </ul>
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.

Whole body FDG-PET scanning is also available as a new nuclear medicine technology for whole body staging and disease assessment. This can be especially helpful in patients with myeloma which produces low levels of M-protein or no protein (non-secretors). FDG is Flouro-Deoxy-Glucose, i.e., sugar which is labeled for nuclear medicine use. Scanning detects areas in which active myeloma incorporates this sugar.

## 2. TRANSPLANTATION

### HIGH DOSE THERAPY (HDT) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION

- 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: unfortunately > 90% of patients relapse.
- Complete remission rates with HDT as a planned part of frontline therapy range from 24-75%.
- Partial remission rates (i.e. > PR) with HDT as frontline range from 75-90%.
- Time to progression (first progression or relapse) is 18-24 months.
- Median overall survival with HDT is in the 4- 5-year range. This is reflected as being statistically superior in the randomized Attal study (1996) and in the MRC study (2003), for example, as well as in the historical case-controlled Nordic Myeloma Study (2000).
- 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 200mg/m<sup>2</sup> 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 pre-para-tive 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 (median survival of 62 months versus 44) of survival at an estimated added cost of \$27,000/year.

#### 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 200mg/ m<sup>2</sup>.

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 including VAD, dexamethasone, thalidomide/dexamethasone, and Cytoxin are discussed above.

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

Part of the decision process for auto transplant involves knowledge of the impact of waiting, with a view to transplant at relapse. Data from

TABLE 10  
TESTS REQUIRED TO MONITOR THERAPY RESPONSES

BLOOD TESTS	<ul style="list-style-type: none"> <li>• Routine blood counts</li> <li>• Chemistry panel</li> <li>• Liver function tests</li> <li>• Myeloma protein measurements (<i>serum protein electrophoresis plus quantitative immunoglobulins</i>)</li> <li>• Serum <math>\beta_2</math> microglobulin</li> <li>• C-reactive protein</li> <li>• Peripheral blood labeling index</li> <li>• Serum erythropoietin level</li> </ul>
URINE	<ul style="list-style-type: none"> <li>• Routine urinalysis</li> <li>• 24-hour urine for measurement of total protein, electrophoresis, and immunoelectrophoresis</li> <li>• 24-hour urine for creatinine clearance if serum creatinine elevated</li> </ul>
BONE EVALUATION	<ul style="list-style-type: none"> <li>• Skeletal survey by X-ray</li> <li>• MRI/CT scan for special problems</li> <li>• Whole body FDG/PET scan if disease status unclear</li> <li>• Bone density measurement (DEXA scan) as baseline and to assess benefit of bisphosphonates</li> </ul>
BONE MARROW	<ul style="list-style-type: none"> <li>• Aspiration and biopsy for diagnosis and periodic monitoring</li> <li>• Special testing to assess prognosis (e.g. look for chromosome 13 abnormalities, immunotyping, LI%)</li> </ul>
OTHER TESTING (SPECIAL CIRCUMSTANCES)	<ul style="list-style-type: none"> <li>• Amyloidosis</li> <li>• Neuropathy</li> <li>• Renal or infectious complications</li> </ul>

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.

### 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.
- 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 not known.
- The results with planned primary tandem transplant (total therapy I and II at the University of Arkansas) have been good. The median overall survival has been 68 months with some groups having even longer survival.
- However, recent comparative studies, including the French randomized studies, have shown benefit predominantly for a subgroup of patients (those who have not achieved 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 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.

TABLE 11  
HIGH-DOSE THERAPY

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

## THE ROLE OF ALLOGENEIC TRANSPLANTATION

- Details of results with allogeneic transplantation have been extensively reviewed.
- Despite medical improvements over the past 2 decades, allogeneic transplant, even with a perfectly matched family member 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 15-20%. In other centers, 20-30% or higher mortality is frequently reported. The pulmonary complications are usually the most critical for myeloma patients.
- 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.
- There is recent interest in non-myeloablative or “mini” allogeneic transplants in myeloma. The intent is primarily to achieve a graft versus myeloma effect with lesser toxicity than with a matched full allogeneic transplant. However, although anti-myeloma effects have been promising, with an 84% response rate in the first 32-patient series, the risks remain high, with substantial acute (45%) and chronic (55%) graft versus host disease reported.

### 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 a promising new approach, which requires further evaluation as part of well-planned clinical trials.
- c. Identical twin, or syngeneic, transplantation is a rare option, which is a safe procedure with good outcome and is recommended 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 can be 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 the past 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 in the prolongation of remission has been observed. The benefit is only 10-15% in terms of prolongation of remission and survival. Differences of 10-15% (e.g. 6-9 months) are hard to prove in clinical studies. Ongoing studies include evaluation of interferon with initial chemotherapy, and the combination of alpha interferon with a variety of agents such as dexamethasone or IL-2 for maintenance. The use of alpha interferon has to be individualized, balancing potential benefits with potential side effects, expense, and inconvenience. Most investigators think that alpha interferon has a definite (although small) role in the management of myeloma.

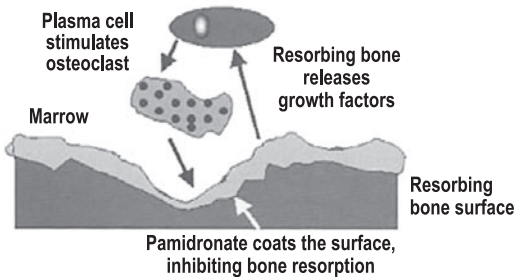
**Prednisone** – It has been difficult to find therapy that can prolong remissions and survival in myeloma without compromising quality of life, as is the case with alpha interferon. However, new studies have supported earlier observations from the 1980s that prednisone is an effective maintenance agent,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

**Thalidomide** – Data are just being gathered to fully assess the role of thalidomide in the maintenance setting. Initial results are promising. It seems that thalidomide alone or combined with steroids in some fashion will be helpful. Peripheral neuropathy is the major concern with long-term use of thalidomide.

## 5. SUPPORTIVE CARE:

**Erythropoietin** – Erythropoietin (e.g. Procrit®) 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 SQ 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. Erythropoietin should only be continued in patients showing clear benefit. Iron supplements may be required to achieve maximum benefit. The newer long-acting erythropoietin product Aranesp® (darbapoietin) is also available for use

FIGURE 5: HOW PAMIDRONATE WORKS



**Bisphosphonates** – Bisphosphonates are a class of chemicals that bind to the surface of damaged bones in patients with myeloma. This binding inhibits the 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 are now available including clodronate, an oral formulation in use in Europe for the treatment of myeloma, 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. One, called ibandronate, is now available in Europe.

Two new concerns have emerged related to chronic bisphosphonate use. The first is kidney damage and the second is a condition called osteonecrosis of the jaw. These two issues have been addressed in detail in other IMF educational materials (Myeloma Minute and Myeloma Today). 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 0.5-1.0 mg/dl, dose and/or schedule adjustments for Aredia or Zometa may be required. For Zometa, one of the simplest adjustments is to extend the infusion time from 15 minutes to 30-45 minutes, which reduces the risk

of renal impairment. As far as osteonecrosis is concerned, the first step is regular dental check-ups. If a problem is found, referral to an expert (e.g. oral surgeon) is strongly recommended. Any major jaw surgery must be avoided until consultation has been sought. Regular, routine dental checkups are recommended. Dental extractions should be avoided until full consultation has been obtained. Infection may require antibiotic therapy.

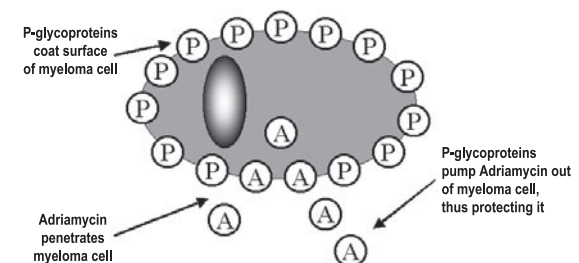
**Antibiotics** – Infections are a common and recurrent problem in patients with myeloma. A careful strategy for infection management is required. Antibiotic therapy should be instituted immediately if active infection is suspected. Use of preventative or prophylactic antibiotics with recurrent infection is controversial. The continuation of prophylactic antibiotics can increase the chance of antibiotic resistance, but it can also reduce the chance of recurrent infective complications. A recent comparative study showed benefit with prophylactic antibiotics used within the first 2 months of induction chemotherapy. The use of high-dose gammaglobulin 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.

## 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 alpha interferon, prednisone, or thalidomide maintenance 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 achieve a second remission with the same therapy that produced the first. This is particularly true for patients in remission for over one year following the initial induction attempt. As an example, a patient who has received MP and has gone into remission for two years can again receive MP induction.

FIGURE 6: MDR MYELOMA CELL



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 VAD is an important consideration in this setting.

**VELCADE® (bortezomib) for relapsing myeloma** – The availability of VELCADE® for relapse treatment is an important step forward. The FDA approved VELCADE® for use in this setting in early 2003. Final results of the 202-patient, multicenter, phase II “SUMMIT” trial of VELCADE® in heavily pretreated (median 6 prior lines of therapy) patients with relapsed and refractory myeloma were presented at ASH in 2002. The response rates, according to the criteria defined by Bladé and confirmed by an independent review committee, are summarized below:

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**RESPONSE TO VELCADE® ALONE IN THE SUMMIT TRIAL**

<b>Response (Bladé criteria)</b>	<b>Percentage of patients</b>
Complete response (IF neg)	4
Complete response (IF pos) <sup>a</sup>	6
Partial Response	17
Minimal response	8
Stable disease	24
<b>Overall response</b>	<b>35%</b>

<sup>a</sup>M-protein not measureable, but still detectable by immunofixation.

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The overall response rate (CR + PR + MR) was 35%. Of note, the median response duration at that time was 12 months and median overall survival was 16 months. Subsequent follow-up has revealed a median response duration in responding patients of 12.7 months. This compares very favorably to the much poorer outcome in refractory patients reported in the literature. Results in earlier-stage disease in the “CREST” study were also presented at ASH. These patients had received a median of three prior regimens, including stem cell transplant in 48%. In the CREST study, overall responses (CR, PR, MR) were 33% and 50% at doses of 1.0 and 1.3 mg/m<sup>2</sup>. These studies were also evaluated using the response criteria of Bladé *et al.* In the Summit phase II study, responses were independent of the number or type of prior therapies and were associated with improved quality of life.

Based upon these promising results, VELCADE® was approved by the FDA for the treatment of 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. At the ASCO meeting in June, 2004, Dr. Paul Richardson presented the results of this randomized phase II trial for relapsed myeloma, which compared bortezomib (VELCADE®) with dexamethasone. This study recruited internationally and was the largest study ever completed in multiple myeloma. At the mandated early interim analysis, bortezomib (VELCADE®) was significantly more effective than dexamethasone. There was a 58% improvement in the median time to progression for the 327 patients receiving bortezomib versus the 330 patients receiving high-dose dexamethasone (p<.0001 for difference). Overall, there was an approximately 30% improvement in survival during the first year with bortezomib (VELCADE®). This is obviously very helpful information in establishing the role for VELCADE® and in future integration of VELCADE® into “standard of care” therapies.

**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. The group at the Royal Marsden Hospital in London has had excellent results using second and third rounds of high-dose melphalan for patients treated in the early to mid 1980s. It is important to note that in this same patient population, the Royal Marsden group has shown that maintenance alpha interferon following high-dose therapy prolongs the quality and duration of the remission.

A full range of supportive care aspects are crucial for the management of MM. 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 MM. This can be difficult until initial disease control is achieved. There is no reason for patients with MM 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.

**TABLE 12**  
**CLINICAL TRIAL PHASES**

I	Early testing to assess 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
V	Usually carried out after FDA approval to assess cost-effectiveness, quality of life impact, and other comparative issues

## 7. NEW AND EMERGING TREATMENTS:

Most new treatments are available in the setting of clinical trials. Clinical trial phases are listed in Table 12. A whole range of agents is entering clinical trials, covering a spectrum from conventional chemotherapy products (e.g. Doxil®) to cytokines (e.g. Avastin™: anti-VEGF), biologic agents (e.g. Betathine), novel agents (e.g. arsenic trioxide [ATO]), as well as heat shock protein inhibitors, gene therapy and vaccine strategies. Patients are encouraged to contact the IMF via telephone or Internet (www.myeloma.org) and to check with their physicians regarding the availability of new clinical trials in their region of the US. The MYELOMA MATRIX, an IMF publication, is available with regular updates and lists all drugs currently in clinical trials. The Mayo Clinic Proceedings (2005) article listed in the references is a very good summary of new therapies

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