

# Multiple Myeloma

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\* This work was supported in part by grant CA 91561-01.

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### 3.1 Introduction

Multiple myeloma is a neoplastic plasma cell dyscrasia (PCD) characterized by a clinical pentad: 1) anemia, 2) a monoclonal protein in the serum or urine or both, 3) abnormal bone radiographs and bone pain, 4) hypercalcemia, and 5) renal insufficiency or failure. With the exception of monoclonal gammopathy of undetermined significance (MGUS), it is the most common PCD, with an incidence of about 4.5 per 100,000 per year in the United States. Solitary plasmacytoma and plasma cell leukemia (PCL) are recognized as separate entities and are much less prevalent. The underlying pathogenesis of the plasma cell malignancies is not well under-

stood but is an area of active investigation. At present, according to WHO (World Health Organization) and REAL (Revised European-American Lymphoma) classification systems, there is only 1 category for multiple myeloma. Results of clinical trials are confounded by this underclassification. Emerging information about the disease, however, will likely change this underclassification.

The interactions among the plasma cells, their antibody product, the local bone and bone marrow environment, and other organs are complex. There is no cure for multiple myeloma, but there are many effective treatments that prolong and improve the quality of life in patients with the disease.

## 3.2 History

### 3.2.1 The Earliest Diagnoses and Diagnostic Methods

Samuel Solley reported the first well-documented case of myeloma in Sarah Newbury in 1844 (mollities ossium) (Kyle 2000). Several years later, William MacIntyre described and recorded the properties of the disease we now call multiple myeloma in Thomas Alexander McBean. Both Drs. MacIntyre and Bence Jones noted and described some of the peculiar urine properties of this same patient. On heating, the urine was found to “abound in animal matter,” which dissolved on the addition of nitric acid but reappeared after cooling. These urinary proteins became known as Bence Jones proteins. MacIntyre and Dalrymple described the postmortem examination of Mr. McBean’s bones. The former described the affected bones as softened and fragile, with their interiors replaced with a soft “gelatinous” blood-red substance. Dalrymple suggested that the disease began in the cancellous bone and extended through the periosteum. The nucleated cells, which formed the bulk of the gelatinous material, were heterogeneous in size and shape, but the majority were round to oval. Many of the larger and more irregular cells frequently contained 2 and often 3 nuclei. The term “multiple myeloma” was coined in 1873 by von Ruzizky who independently described a similar patient to emphasize the multiple bone tumors that were present.

In 1889, Professor Otto Kahler described a case involving a 46-year-old physician with multiple myeloma and executed a major review of the disease. He described the skeletal pain, albuminuria, pallor, anemia, a precipitable urinary protein, and the findings on necroscopy and linked these findings as part of a clinical syndrome, which bears his name (multiple myeloma is also known as Kahler disease).

In 1898 Weber postulated that bone marrow was the site of production of the Bence Jones protein. Wright emphasized that multiple myeloma arose specifically from plasma cells of the marrow in 1933. In 1917 and 1921, respectively, Jacobson and Walters recognized Bence Jones proteins in the bloodstream and concluded that the Bence Jones protein was probably derived from blood proteins through the action of the abnormal cells in the bone marrow.

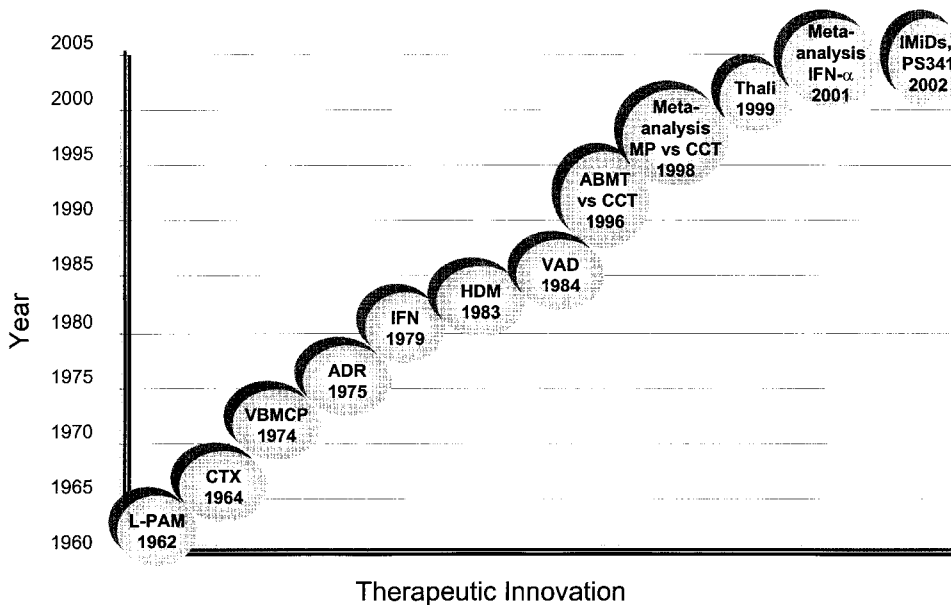
In 1922 Bayne-Jones and Wilson identified 2 similar but distinct groups of Bence Jones proteins by immuniz-

ing rabbits with Bence Jones proteins from patients. Using the Ouchterlony test, Korngold and Lipari showed that antisera to Bence Jones protein also reacted with myeloma proteins. The 2 classes of Bence Jones proteins have been designated kappa and lambda as a tribute to these 2 men. In 1962, Edelman and Gally showed that the light chains prepared from an IgG monoclonal protein and the Bence Jones protein from the same patient’s urine were identical. Longsworth et al. applied electrophoresis to the study of multiple myeloma and described the tall narrow-based “church spire” peak. Paper electrophoresis was supplanted by filter paper in 1957. Most recently, high-resolution electrophoresis on agarose gel is used in most laboratories. Immunoelectrophoresis and immunofixation or direct immunoelectrophoresis make it possible to detect small monoclonal light chains not recognizable on electrophoresis.

In 1928, Geschickter and Copeland reported on the largest case series of multiple myeloma – 13 cases – and reviewed the 412 cases reported in the literature since 1848. They documented a higher incidence in men than women and an overall survival of about 2 years. They emphasized 6 features: 1) involvement by the tumor of the skeletal trunk, 2) pathologic fractures of the ribs, 3) Bence Jones proteinuria in 65% of cases, 4) backache with early paraplegia, 5) anemia in 77% of cases, and 6) chronic renal disease. They did not note abnormalities of blood protein or increased erythrocyte sedimentation rate (Kyle 2000). In 1931, Magnus-Levy described amyloidosis as a complication of multiple myeloma. Salmon, Durie, and Smith developed methods to quantitate the total body burden of tumor cells and to stage patients (Durie and Salmon 1975) in the 1970s.

### 3.2.2 The Earliest Treatments for Multiple Myeloma

In 1947 Snapper reported that stilbamidine along with a low animal protein diet relieved myeloma pain in 14 of 15 patients (Kyle 2000). Subsequent studies did not confirm a benefit. Urethane was believed to be effective until 1966. It was first used in the treatment of multiple myeloma by Alwall in 1947 and then by Loge and Rundles in 1949. Their early observations were encouraging, and the use became widespread. Toxic effects included severe anorexia, nausea, vomiting, cytopenias, and hepatic damage. In 1966, however, Holland et al. published



**Fig. 3.1.** Landmark therapeutic innovations. *ABMT*, autologous bone marrow transplant; *ADR*, doxorubicin; *CCT*, conventional chemotherapy; *CTX*, cyclophosphamide; *HDM*, high-dose melphalan; *IFN- $\alpha$* , interferon- $\alpha$ ; *IMiDs*, immunomodulatory derivatives of thalido-

mide; *L-PAM*, melphalan; *MP*, melphalan and prednisone; *PS341*, proteasome inhibitor; *Thali*, thalidomide; *VAD*, vincristine, doxorubicin, and dexamethasone; *VBMCP*, vincristine, BCNU, melphalan, cyclophosphamide, and prednisone (M-2 regimen).

the results of a randomized controlled trial of urethane versus placebo in 83 patients with symptomatic multiple myeloma. The median overall survival was higher in the placebo group: previously untreated patients had a median survival of 12 or 5 months depending on whether they received placebo or urethane.

In 1950, Thorn et al. reported the first observations on the beneficial effects of adrenocorticotrophic hormone on myeloma. During that decade, it was recognized that adrenocorticotrophic hormone, cortisone, and prednisone were all useful agents in patients with multiple myeloma. Corticosteroids decreased bone pain, improved hypercalcemia, increased hemoglobin values, and decreased abnormal serum and urine globulin concentrations.

In 1958 Blokhin et al. reported benefits in 3 of 6 patients with multiple myeloma who were treated with sarcocysin (a racemic mixture of the *d*- and *l*-isomers of phenylalanine mustard). Subsequently, the *d*- and *l*-isomers were tested separately, and the anti-myeloma activity was found to reside in the *l*-isomer, melphalan. In 1962, Bergsagel et al. reported significant improvement in 14 of 24 patients with multiple myeloma with the use of melphalan; this activity was quickly substan-

tiated by others (Bergsagel et al. 1967). Similar activity was noted with cyclophosphamide. Subsequently, interferon- $\alpha$ , doxorubicin, carmustine, and thalidomide have each been reported to have activity as a single agent in myeloma (Alberts et al. 1976; Myeloma Trialists' Collaborative Group 2001) (Fig. 3.1).

### 3.3 Incidence and Epidemiology

#### 3.3.1 Epidemiology of Myeloma

There are approximately 14,400 new cases of multiple myeloma diagnosed each year and 11,200 deaths. SEER (Surveillance, Epidemiology, and End Results) data incidence age-adjusted rates from 1992 through 1998 show an overall incidence of 4.5 per 100,000 per year, with the incidence among whites at 4.2 per 100,000 per year and among blacks at 9.3 per 100,000 per year. Male-to-female ratio is 1.4 to 1. The median age at diagnosis of myeloma is 71 years. Mortality rates are consistently higher among men than women and among blacks than whites in each age group. Myeloma accounts for 1% of all malignancies and 10% of all hematologic malignan-

cies in whites and 20% in African Americans. International mortality data reveal that the highest rates of myeloma occur in Northern Europe, North America, Australia, and New Zealand and the lowest rates are in Japan, Yugoslavia, and Greece.

### 3.3.2 Etiologic Factors

#### 3.3.2.1 Radiation Exposures

Reports of increased myeloma incidence and mortality among Japanese atomic bomb survivors have suggested an association between ionizing radiation and multiple myeloma. Evaluations of cancer incidence and mortality among Japanese atomic bomb survivors demonstrated an increased risk of multiple myeloma with increasing radiation dose. However, with an additional 12 years of follow-up from the previous comprehensive report, the findings of an increased myeloma risk associated with atomic bomb irradiation were refuted.

An excess of myeloma deaths was reported among American radiologists more than 40 years ago, but subsequent reports have been contradictory. For example, increases in multiple myeloma incidence and mortality have been observed among British military men who participated in atmospheric nuclear weapons testing but not among New Zealand military who participated in similar nuclear weapons testing.

Diagnostic x-ray exposure has not been linked clearly with multiple myeloma, and most epidemiologic studies have reported no association with diagnostic x-rays. Studies of the effects of therapeutic irradiation on myeloma risk have shown conflicting results.

#### 3.3.2.2 Workplace Exposures

Several epidemiologic studies have evaluated the risk of myeloma among agricultural workers, with positive associations reported by many but not all of the studies. Workers in various metal occupations and industries have been reported to have an increased myeloma risk. There is no evidence of a link between benzene exposure and myeloma.

#### 3.3.2.3 Lifestyle Factors

There is no evidence of a link between cigarette smoking or alcohol consumption and the development of

multiple myeloma. There may be a higher risk among people whose diets contain large quantities of liver and butter and a lower risk among people who consume large amounts of cruciferous vegetables, fish, and vitamin C supplements. Obesity, lower socioeconomic status, and personal use of dark hair dyes appear to be risk factors for multiple myeloma.

#### 3.3.2.4 Precursor Medical Conditions

MGUS is considered a potential precursor condition for multiple myeloma. In a long-term study of prognosis in MGUS, Kyle and colleagues (2002) identified 1,384 patients in southeastern Minnesota in whom MGUS was diagnosed. During 11,009 person-years of follow-up, 115 of the 1,384 MGUS patients progressed to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma. The risk of progression of MGUS to multiple myeloma-related disorders is thus about 1% per year.

Repeated or chronic antigenic stimulation of the immune system may lead to myeloma. Several case-control studies have suggested that myeloma risk is associated with past history of inflammatory conditions, connective tissue disorders, autoimmune illnesses, and allergy-related disorders, but other studies of individuals with these conditions have not been confirmatory.

Patients with human immunodeficiency virus may have an increased likelihood of developing myeloma. In addition, myeloma and hepatitis C may be associated. Human herpesvirus 8 has been suggested as a possible etiologic agent (Rettig et al. 1997), but it has not been confirmed.

Familial clusters of myeloma among first-degree relatives have been documented. Epidemiologic studies have reported higher frequencies of myeloma among cases compared with controls.

## 3.4 Pathogenesis and Pathophysiology

To date no single molecular defect can account for the pathogenesis of multiple myeloma. Malignant plasma cells are long-lived cells, typically with low proliferative rates and labeling indices. A postgerminal cell origin is indicated by their somatically hypermutated rearranged immunoglobulin genes. Abnormalities of signaling pathways, apoptotic mechanisms, bone marrow micro-

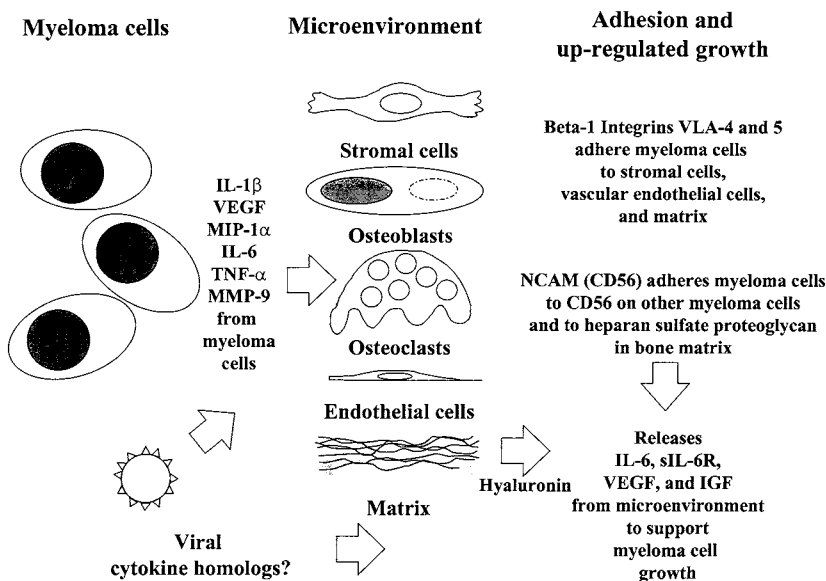
environment, and cell cycle have been identified. Factors including level of gene expression, protein expression, and gene product phosphorylation status of cell cycle molecules may all be relevant for propagation of the malignant plasma cells. Extracellular signaling alterations include changes in stromal cell, osteoblast, osteoclast, vessel endothelial cell, and immune cell interactions. These changes may in turn result in activation, adhesion, and cytokine production that fuel myeloma cell proliferation and survival.

### 3.4.1 Cytokines and Cell Signaling

Interleukin (IL)-6 is among the most important proliferation and survival factors in myeloma. Predominantly produced by the bone marrow stromal cells – macrophages, fibroblasts, osteoblasts, osteoclasts, and monocytes (Fig. 3.2) – it serves both as a growth factor and as an antiapoptotic factor. In the majority of cases, myeloma cells and cell lines are capable of producing IL-6 and the IL-6 receptor, resulting in autocrine stimulation. IL-6 transmits messages intracellularly through the signal-transducing protein gp130, which can activate 2 pathways: the JAK-STAT pathway and the Ras-MAP kinase pathway (Hallek et al. 1998). Through the former pathway, which includes JAK-2 and STAT3, the antiapoptotic proteins Mcl-1 and Bcl-X<sub>L</sub> are up-regulated; through the latter pathway, transcription factors such

as ELK-1, AP-1, and NF-IL-6 are up-regulated. NF-kap-paB and IL-6 may also mediate increases in the antiapoptotic proteins Bcl-2, Mcl-1, and Bcl-X<sub>L</sub>. The overall effect of these pathways is prevention of apoptosis and enhancement of multiple myeloma proliferation. In addition, the constitutive activation of STAT3 may also be important in the pathogenesis of multiple myeloma, independent of IL-6. Finally, CD40 activation of myeloma cells can alter cell surface phenotype, triggering auto-crine IL-6 secretion regulating myeloma cell cycle in a p53-dependent fashion.

Other cytokines and growth factors produced by myeloma and stromal cells that maintain myeloma growth include IL-1 $\beta$  (Lacy et al. 1999), vascular-derived endothelial growth factor (VEGF), insulin-like growth factor (IGF), and tumor necrosis factor- $\alpha$  (Dalton et al. 2001). Aberrant expression of IL-1 $\beta$  may be a critical step in the transition of MGUS to multiple myeloma. IL-1 $\beta$  up-regulates production of IL-6, changes expression of cell adhesion molecules, and has been shown to have osteoclast-activating factor activity. Myeloma cells are capable of expressing and secreting VEGF and responding to the cytokine in an autocrine fashion. Moreover, stromal and microvascular endothelial cell exposure to VEGF induces an increase in IL-6 secretion, which then further stimulates myeloma cells. IGF, which is believed to signal through the phosphatidylinositol-3'-kinase (PI-3K) pathway, is capable of directly stimulating myeloma cell growth and enhancing myeloma cell respon-



**Fig. 3.2.** Paracrine myeloma cell growth model. Putative pathogenic mechanisms in myeloma. IGF, insulin-like growth factor; IL, interleukin; MIP, macrophage inflammatory factor; MMP, metalloproteinase; NCAM, neural cell adhesion molecule; TNF, tumor necrosis factor; VEGF, vascular-derived endothelial growth factor; VLA, very late antigen.



siveness to IL-6 through mitogen-activated protein (MAP) kinase and also inhibiting apoptosis by increasing expression of BAD.

### 3.4.2 Bone Marrow Microenvironment

There is a synergistic, pathologic relationship between myeloma cells and the cells comprising the bone marrow microenvironment, including fibroblasts, osteoblasts, and osteoclasts. High levels of IL-6 are produced in vitro by the stromal cells of the marrow of myeloma patients. The IL-6 serves as a growth and survival factor for benign and malignant plasma cells, which thereby produce IL-1 $\beta$ , VEGF, and macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ). In turn, IL-1 $\beta$  and MIP-1 $\alpha$  regulate and activate osteoclasts.

A cell adhesion molecule belonging to the immunoglobulin superfamily, CD56 (N-CAM), is strongly expressed in most plasma cells of myeloma patients and is believed to play a role in myeloma homing and cell adhesion to the marrow. In a majority of patients, increased levels of the adhesion molecules lymphocyte function-associated antigen (LFA)-3, LFA-1 (CD11a), and very late antigen-4 (VLA-4) are expressed on myeloma cells. VLA-4 may act to bind myeloma cells to fibronectin in bone marrow, which under appropriate conditions can significantly increase IL-6 production by stroma (Dalton et al. 2001). Cell-cell contact between marrow stromal cells and myeloma cells via VCAM-1 and  $\alpha_4\beta_1$ -integrin enhances production of osteoclast-stimulating activity.

The endothelial microvascular environment has also been shown to be important in multiple myeloma biology. VEGF plays an important role in angiogenesis by acting as a potent inducer of vascular permeability as well as serving as a specific endothelial cell mitogen. Plasma cells in the bone marrow from multiple myeloma patients express VEGF, which can thereby interact with the Flt-1 and KDR high-affinity VEGF receptors highly expressed on bone marrow myeloid and monocytic cells surrounding the tumor.

### 3.4.3 Cell Cycle

Regulatory signals underlying proliferation of myeloma cells include increased cyclin D1 expression, hypermethylation of the cyclin-dependent kinase (CDK)

pathway regulatory gene p16, mutations of the *ras* oncogene, and loss of *p53* (Hallek et al. 1998).

Approximately one-third of myeloma patients have up-regulation of cyclin D1 by immunohistochemistry; these same patients' plasma cells tend to have higher proliferative rate (Rajkumar and Greipp 1999). Particularly, the t(11;14)(q13;q32) translocation, which juxtaposes the immunoglobulin heavy chain promoter and the cyclin D1 gene, is seen in approximately 25% of multiple myeloma patients but is not typically associated with a worse prognosis.

Both p15 and p16 are important cell cycle inhibitors that suppress cell proliferation through inhibition of CDK4 or CDK6 or both, thereby preventing the phosphorylation of the retinoblastoma gene (*RB*). Although large deletions of p15 and p16 are rare in myeloma, selective methylation of these genes, a form of transcriptional inactivation, occurs in as many as 67% and 75% of cases, respectively. Most data suggest that hypermethylation of p15 or p16 is associated with disease progression.

K- and N-*ras* mutations have been described in 25% to 100% of newly diagnosed multiple myeloma patients, depending on the technique used for detection. A p53 tumor suppressor gene deletion is present in less than one-third of plasma cells from newly diagnosed myeloma patients and mutations are even less common. Dysregulation of *c-myc* appears to be caused principally by complex genomic rearrangements that occur during late stages of multiple myeloma progression. The *c-myc* protein and *c-myc* RNA are overexpressed in about 25% of multiple myeloma patients. Rearrangements of the *c-myc* gene are present in about 15% of patients with multiple myeloma or primary PCL.

## 3.5 Clinical Manifestations

The symptoms of multiple myeloma may be nonspecific (Table 3.1). They may include fatigue, bone pain, easy bruisability and bleeding, and recurrent infections, which may be manifestations of underlying anemia, hypercalcemia, lytic bone lesions, hyperviscosity, thrombocytopenia, and hypogammaglobulinemia. Weakness, infection, bleeding, and weight loss are reported in as many as 82%, 13%, 13%, and 24% of patients, respectively (Kapadia 1980; Kyle et al. 2003). Hypercalcemia is present in 18% to 30% of patients. One- to two-thirds

**Table 3.1.** Symptoms and signs of multiple myeloma at presentation

Symptom or sign	Patients, %
Spontaneous bone pain	66
Fatigue	32
Weight loss (> 20 pounds)	12
Infection and bleeding	<15
Paresthesia	5
“Tumor fever”	<1
M protein in serum or urine	97
Lytic lesions, osteoporosis, or fracture on plain radiograph	79
Hemoglobin <12 g/dL	73
Creatinine >2 mg/dL	19
Calcium >11 mg/dL	13
Viscosity >4 cP	<7

Data from Kyle et al. (2003).

of patients present with spontaneous bone pain. “Tumor fever” is present in less than 1% of presenting patients.

### 3.5.1 Anemia

The most common clinical feature of multiple myeloma is anemia. A hemoglobin concentration of less than 12 g/dL occurs in 40% to 72% of patients at presentation (Kyle et al. 2003). The anemia is normochromic, normocytic in most patients, but macrocytosis may also be observed. In the presence of high concentrations of serum immunoglobulin, rouleau formation may be observed on peripheral blood smear (Fig. 3.3). The combination of anemia and hyperproteinemia leads to marked increase of the erythrocyte sedimentation rate in more than 90% of cases.

The anemia is related partially to direct infiltration and replacement of the bone marrow. Hemoglobin concentration is also correlated with the percentage of myeloma cells in S phase, suggesting that the bone marrow cytokine milieu permissive for myeloma cell proliferation is not conducive to efficient erythropoiesis. Cytokines, like tumor necrosis factor- $\alpha$  and IL-1, may inhibit erythropoiesis. Fas ligand-mediated erythroid apoptosis is also increased in patients with myeloma. Finally, rel-

ative erythropoietin deficiency from myeloma-induced renal insufficiency also contributes to the observed anemia.

### 3.5.2 Monoclonal Proteins

The M protein (M component, myeloma protein, or M spike) is a hallmark of the disease in that 97% of myeloma patients have either an intact immunoglobulin or a free light chain that can be detected by protein electrophoresis, immunoelectrophoresis, or immunofixation studies of the serum or urine (Fig. 3.4) (Kyle et al. 2003). Monoclonal proteins are used to calculate myeloma tumor burden and kinetics, to stage myeloma patients, and to document their response to treatment.

An M protein represents overproduction of a homogeneous immunoglobulin or immunoglobulin fragment. In a series of 1,027 newly diagnosed cases of myeloma, the immunoglobulin type was IgG, IgA, IgD, and free light chain only (Bence Jones myeloma) in 52%, 20%, 2%, and 16% of cases, respectively (Kyle et al. 2003). Less than 1% of myeloma cases are IgM; most IgM cases are MGUS, lymphoma, Waldenström macroglobulinemia, or primary systemic amyloidosis. Ninety-three percent of patients have a monoclonal protein detected in their serum. About 70% have a monoclonal protein – or fragment thereof – detected in the urine.

### 3.5.3 Bone Disease

Approximately one-third to two-thirds of patients present with bone pain (Kapadia 1980; Kyle et al. 2003). Myeloma bone disease is a major source of morbidity in patients and may present as an area of persistent pain or as a vague migratory bone pain, often in the lower back and pelvis. The type, location, and duration of the pain are not characteristic. It may be sudden in onset, especially when associated with a pathologic fracture. Persistent localized pain or tenderness of sudden onset is usually referable to a pathologic fracture.

A myelomatous lesion may extend through the cortex of a vertebral body and cause either nerve root or spinal cord compression. More commonly, the myeloma disturbs the mechanical integrity of a vertebral body, resulting in compression fracture and pain (Fig. 3.5 D). Occasionally, there may be retropulsion of either plasmacytoma or bony fragments into the spinal canal, again causing neurologic deficit.



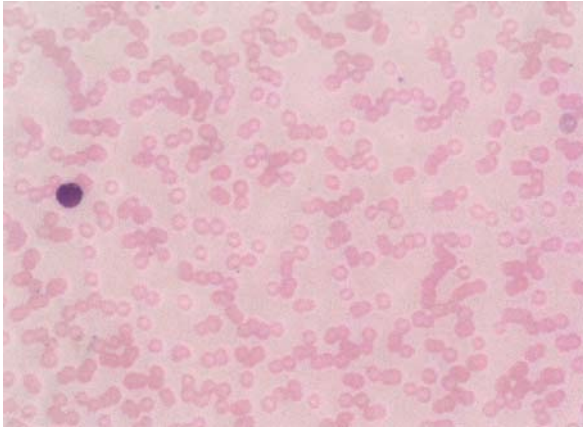


Fig. 3.3. Rouleaux

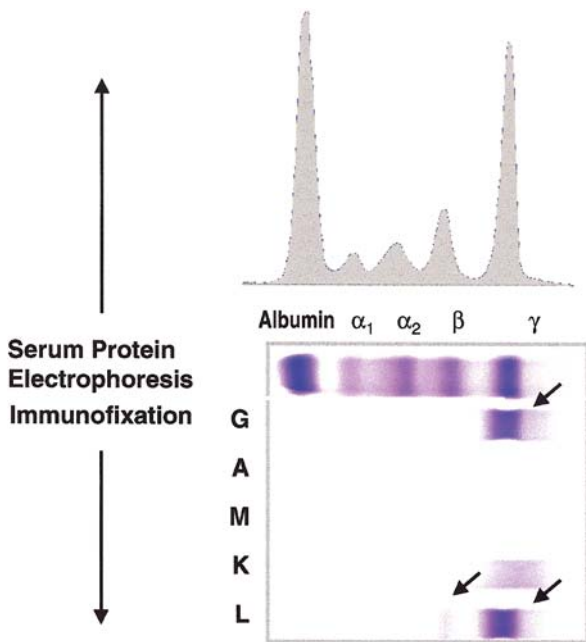


Fig. 3.4. Serum protein electrophoresis patterns and immunofixation patterns

Approximately 75% of patients have punched-out lytic lesions, osteoporosis, or fractures on conventional radiography. The vertebrae, skull, ribs, sternum, proximal humeri, and femora are involved most frequently (Kapadia 1980; Kyle et al. 2003) (Fig. 3.5). A small subset of patients have de novo osteosclerotic lesions (Dispenzieri et al. 2003), but in general osteosclerosis is seen after therapy in a minority of patients and may serve as a marker of healing.

Because myelomatous bone lesions are characteristically lytic, conventional radiography is superior to technetium-99m bone scanning. About twice as many myelomatous bone lesions are detected by radiograph as by bone scan; an exception to this general finding is at the lumbar spine and the rib cage, where the 2 methods are equally reliable. The role of fluorodeoxyglucose positron emission tomography is yet to be defined.

Computed tomography and magnetic resonance imaging (MRI) are more sensitive than conventional radiography. Both reveal specific lesions in 40% of stage I myeloma patients. The presence of lacunae larger than 5 mm with trabecular disruption on computed tomography appears to be sensitive and specific for myeloma. This information may be useful in distinguishing between senile and myelomatous osteoporosis and compression fracture.

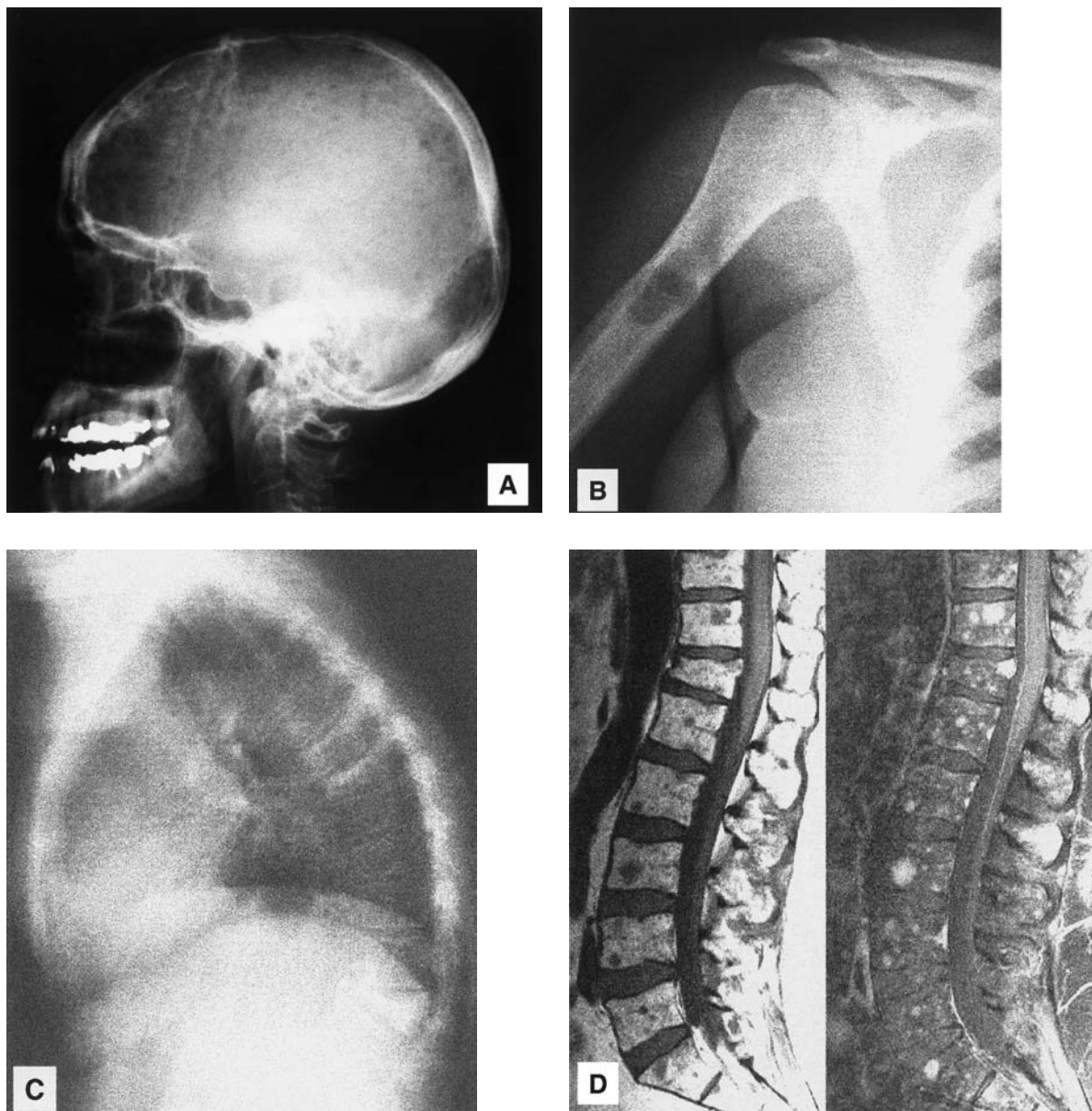
The finding of diffusely decreased signal intensity and a multinodular appearance on MRI may also be useful for the same indication. Among asymptomatic multiple myeloma patients with normal radiographs, 50% have tumor-related abnormalities on MRI of the lower spine. MRI is superior to radiographs for lesion detection in the pelvis and the spine, but overall it is inferior for detecting overall bone involvement. Given the expense of MRI, it cannot be recommended for routine clinical use in all symptomatic patients.

### 3.5.4 Hypercalcemia

Rates of hypercalcemia at presentation have been decreasing in the last few decades, suggesting earlier diagnosis (Kapadia 1980; Kyle et al. 2003). Incidence rates of hypercalcemia at diagnosis are 18% to 30%, and about 13% have concentrations greater than 11 mg/dL. Patients may complain of fatigue, constipation, nausea, or confusion. Hypercalcemia can precipitate and aggravate renal insufficiency. The inorganic phosphorus is rarely decreased, except in cases of acquired Fanconi syndrome.

### 3.5.5 Renal Insufficiency

Approximately 25% of myeloma patients have a serum creatinine value greater than 2 mg/dL at diagnosis. Another 25% have a mildly elevated creatinine value (Kapadia 1980; Kyle et al. 2003). Contributing factors to renal insufficiency include hypercalcemia, free light chain



**Fig. 3.5** A. Skull, punched-out lesions . B–D. B, Humerus, lytic lesion. C, Compression fractures, osteopenia, and kyphosis. D, MRI, bone marrow infiltration, compression fracture, and extradural extension

extending from thoracic levels T6-T9 (T1 with gadolinium and T2 images)

proteinuria, dehydration, hyperuricemia, and nephrotoxic drugs (MRC Working Party on Leukaemia in Adults 1984).

The pathologic lesion of myeloma kidney is the presence of monoclonal light chains in the tubules in the form of dense, often laminated, tubular casts. These casts contain albumin and Tamm-Horsfall protein. Light chains are normally passed through the glomeruli and reabsorbed and catabolized in the nephron's proximal tubules. It is postulated that these systems become overwhelmed, and casts result. The most common abnormal renal findings on autopsy of 60 patients with myeloma were tubular atrophy and fibrosis (77%), tubular hyaline casts (62%), tubular epithelial giant cell reaction (48%), and nephrocalcinosis (42%). Acute and chronic pyelonephritis were observed in 20% and 23% of cases, respectively. Plasma cell infiltrates and amyloid may be observed in 10% and 5% of cases, respectively (Kapadia 1980). Rarely, myeloma may be associated with acquired Fanconi syndrome.

An important feature of myeloma kidney is that it is primarily a tubular, rather than a glomerular, disease. Glomerular function is preserved initially, and there is a predominance of immunoglobulin light chain protein in the urine instead of the nonspecific protein loss observed in glomerular disease. This feature helps predict the renal lesion: a free light chain predominance is consistent with myeloma kidney, whereas nonspecific protein loss (ie, mostly albumin) is more compatible with primary systemic amyloidosis, light chain deposition disease of the kidney, or proteinuria unrelated to the plasma cell dyscrasia.

### 3.5.6 Infection

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Patients with multiple myeloma are at high risk for bacterial infections and for dying of overwhelming bacteremia. During the first 2 months after initiating chemotherapy the infection incidence is as high as 4.68 infections per patient-year but decreases to 0.44 to 0.49 per patient-year in those reaching plateau phase. Serum creatinine value greater than or equal to 2 mg/dL is a risk factor for infection.

At disease onset, infections with encapsulated organisms like *Streptococcus pneumoniae* and *Haemophilus influenzae* are most common. After diagnosis, the proportion of infections due to gram-negative bacilli and *Staphylococcus aureus* increases markedly, and they

are responsible for more than 90% of deaths from infection.

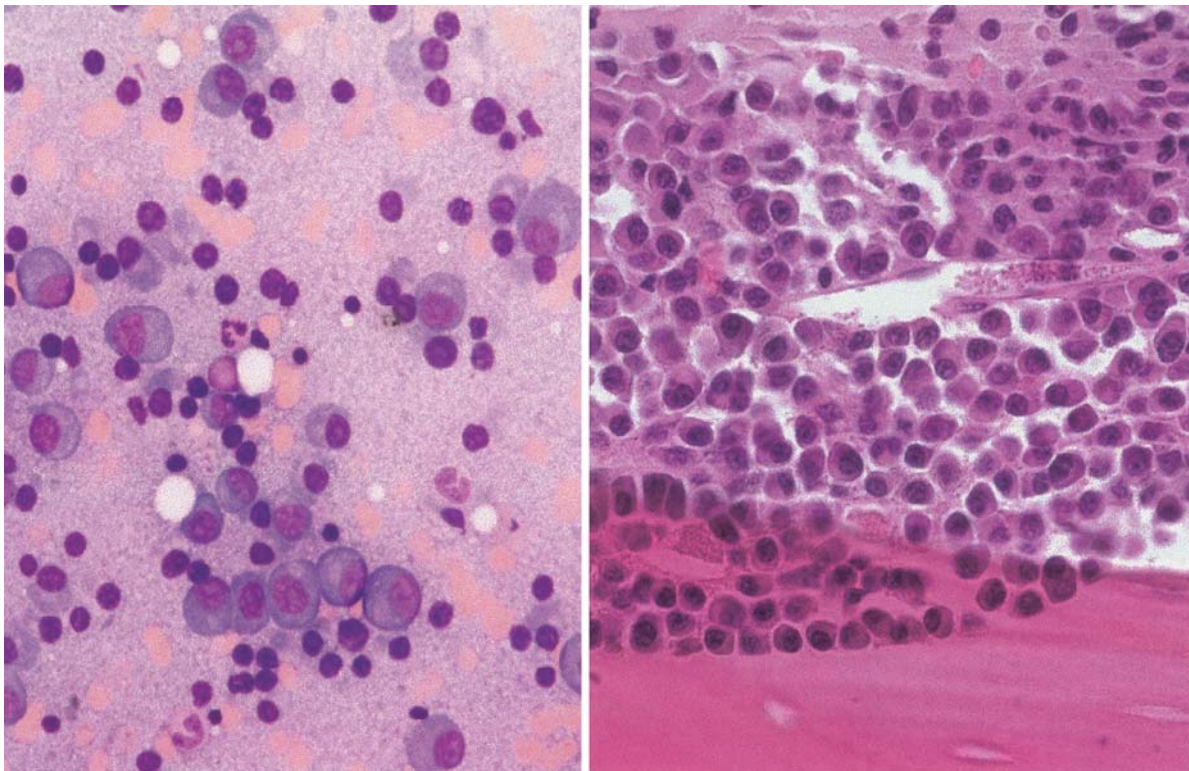
### 3.5.7 Bone Marrow Pathologic Features

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There is a complex interaction among the malignant clone, its surrounding stromal cells, and the remaining immune cells within the bone marrow. The morphologic and immunologic phenotypes of myeloma cells can vary, and they often resemble normal plasma cells. Plasma cells are at least 2 to 3 times the size of peripheral lymphocytes and are round to oval, with one or more eccentrically placed nuclei (Fig. 3.6). The nucleus, which contains either diffuse or clumped chromatin, is displaced from the center by an abundance of rough-surfaced endoplasmic reticulum – the site of specialized immunoglobulin synthesis. There is a perinuclear clear zone that is the site of the Golgi apparatus. Intranuclear and cytoplasmic inclusions are not uncommon. Derangements of immunoglobulin secretion are responsible for an assortment of cytologic aberrations, including flaming cells, Mott cells, Russell bodies, and Gaucher-like cells. Flaming cells are plasma cells that have intensely eosinophilic cytoplasm with a magenta or carmine coloring of their margins, which is caused by plugging of peripheral secretory channels by precipitated immunoglobulin or immunoglobulin fragments. These cells are most commonly seen in IgA myeloma. Thesauocytes are large flaming cells with a pyknotic nucleus that is pushed to the side. Mott cells (grape cells or morula forms) are plasma cells filled with dense spherical immunoglobulin inclusions; these inclusions are colorless, pink, or blue. Other inclusions are Russell bodies and their intranuclear counterparts (intranuclear dense bodies); these appear cherry red and can be as large as several microns in diameter. Gaucher-like cells are not uncommon in myeloma infiltrates; these cells are macrophages laden with sphingolipids released by the dying plasma cells. None of these inclusions are specific for malignancy nor do they have prognostic value.

In myeloma, there is often discordance between the nucleus and cytoplasm, the former appearing immature and the latter highly differentiated. About 20% of myeloma cases have plasmablastic morphology: a diffuse chromatin pattern, nucleus >10 mm or nucleolus >2 mm, relatively less abundant cytoplasm, and a concentrically placed nucleus with little or no hof (Rajku-





**Fig. 3.6.** Bone marrow: normal plasma cells and sheets

mar and Greipp 1999). Both diffuse and nodular infiltration patterns can be observed, although the former is more common. Myeloma cells are commonly present in cords around bone marrow microvessels. Mild marrow fibrosis may be observed in as many as 27% of cases; extensive fibrosis is rare. Less than 1% of cases have an extensive idiopathic granulomatous reaction.

The immunophenotype of myeloma cells is complex. In general, myeloma cells are CD45 negative and CD38 and CD138 positive. CD19 and CD20 are earlier B-cell antigens that are variably expressed on myeloma cells. CD56 is strongly positive in as many as three-quarters of myeloma cases, and CD56-negative myeloma cells tend to be present in more aggressive disease, such as end-stage myeloma or PCL. Other surface antigens like CD10 (CALLA), CD28, *c-kit*, and CD20 are present on a minority of patients' myeloma cells.

The labeling index of bone marrow plasma cells can be useful to identify plasma cell clonality and rate of division. This assay has some value in differentiating

MGUS from myeloma and indolent myeloma from active myeloma. In general, myeloma is a low growth fraction tumor with only a small percentage of myeloma cells in the S phase of the cell cycle at any given time.

### 3.5.8 Hemostasis in Myeloma

Multiple myeloma can be associated with hemostatic abnormalities, more often bleeding than thrombosis. Bleeding as a complication of myeloma may be present in as many as one-third of patients and is related to thrombocytopenia, uremia, hyperviscosity, and interference with coagulation factors. The association with thrombosis is less clear because coexisting old age and immobility confound interpretation of thrombosis rates.

Fewer than 7% of myeloma patients have a viscosity greater than 4 (Kyle et al. 2003). Symptoms of hyperviscosity include bleeding (particularly of the oronasal

areas), purpura, dyspnea, decrease in visual acuity from retinopathy, neurologic symptoms, expanded plasma volume, and congestive heart failure. Most patients become symptomatic when the serum viscosity is 6 or 7 centipoise (normal is less than or equal to 1.8 centipoise).

Myeloma proteins may also interact with coagulation proteins. The immunoglobulin may interfere with fibrin monomer aggregation or serve as a specific inhibitor of thrombin, von Willebrand factor, or factor VIII. Nonspecific inhibitors may also be present, but unlike the specific inhibitors they do not correlate with clinical bleeding. Depression of clotting factors II, V, VII, VIII, X, and fibrinogen has been described.

At the opposite hemostatic extreme, thrombosis risk may be increased in myeloma patients. Individual cases of aberrance have been reported. Paraproteins have been shown to be responsible for lupus anticoagulants, acquired protein S deficiency, acquired activated protein C resistance, and inhibition of tissue plasminogen activator.

### 3.5.9 “Acute Terminal Phase of Plasma Cell Myeloma” and Cause of Death

Bergsagel and Pruzanski described the “acute terminal phase” of patients with myeloma, which they observed in about one-third of their preterminal patients. This syndrome is characterized as rapidly progressive disease with an unexplained temperature and pancytopenia with a hypercellular marrow. Extramedullary plasmacytomas may also occur. As disease progresses, and at autopsy, cutaneous, visceral, and even meningeal involvement is possible. Besides “progressive disease,” the most frequent causes of death are infection in 24% to 52% and renal failure in about 20%. Acute leukemia, myelodysplastic syndrome, and hemorrhage are the cause of death in a minority of patients (Kapadia 1980). In one autopsy series, 85% of patients had evidence of either bacterial or fungal infection and myelomatous involvement was found in the spleen, liver, lymph nodes, and kidneys in 45%, 28%, 27%, and 10% of patients, respectively. Other less frequent areas of myelomatous involvement were the lung, pleura, adrenal glands, pancreas, and testis (Kapadia 1980).

## 3.5.10 Special Cases of Myeloma

### 3.5.10.1 Nonsecretory Multiple Myeloma

Nonsecretory multiple myeloma accounts for 1% to 5% of myeloma cases (Bladé and Kyle 1999). More than 85% of cases have a cytoplasmic monoclonal protein when immunoperoxidase or immunofluorescence studies are performed; in the remainder, no monoclonal protein can be detected in the cytoplasm. Individuals in this latter group are “nonproducers.” From a clinical standpoint, both are referred to as “nonsecretory.” With more sensitive testing like immunofixation and free light chain assay (Drayson et al. 2001), many of these “nonsecretory” patients are found to be low secretors or oligosecretory.

At presentation, hypercalcemia and anemia may be present (Bladé and Kyle 1999). A reduction in background immunoglobulins is common. There is minimal to no risk of myeloma kidney. Lytic bone disease is present in most patients. Median survival of these patients is at least as good as for those with secretory myeloma. Response is difficult to document, but with the new serum assays, quantitation of free light chain is possible in about two-thirds of these patients (Drayson et al. 2001).

### 3.5.10.2 Immunoglobulin D Myeloma

IgD myeloma accounts for about 2% of all cases of myeloma. The presence of a monoclonal IgD in the serum usually indicates myeloma, but there have been 3 cases of IgD MGUS documented (Bladé and Kyle 1999). Patients with IgD myeloma generally present with a small band or no evident M spike on serum protein electrophoresis. Their clinical presentation is most similar to that of patients with Bence Jones myeloma (light chain myeloma) in that they both have higher incidences of renal insufficiency and coincident amyloidosis as well as a higher degree of proteinuria than in IgG or IgA myeloma. With an incidence of 19% to 27%, extramedullary involvement is more prevalent in patients with IgD myeloma. Though initial reports suggested that survival with IgD myeloma was inferior to that with other forms of myeloma, in the Mayo Clinic series in patients diagnosed after 1980, this was not the case.

### 3.5.10.3 Immunoglobulin E Myeloma

IgE myeloma is a rare form of myeloma. A disproportionate number of cases are PCL, although the sample size is small, with only about 40 cases of IgE myeloma reported in the literature.

## 3.6 Diagnosis

The definition of multiple myeloma has unfortunately not been a static one. In 1973, the Chronic Leukemia-Myeloma Task Force set forth guidelines for the diagnosis of myeloma (Table 3.2). These criteria, which by today's standards are not stringent, have been replaced by a more modern definition (Table 3.2) (Kyle and Greipp 1980). In the last 3 decades, the terms and definitions of MGUS, smoldering myeloma, indolent myeloma, and symptomatic multiple myeloma (Alexanian 1980; Kyle and Greipp 1980) have evolved and will be replaced by the following expressions: MGUS, inactive (smoldering) myeloma, and active (or symptomatic) myeloma (Kyle et al. 2003) (Fig. 3.7).

This internationally accepted diagnostic classification schema is derived from more than 4 decades of ex-

**Table 3.2.** Chronic Leukemia-Myeloma Task Force definition of multiple myeloma 1973

If M protein present in serum or urine, 1 or more of the following must be present:

Marrow plasmacytosis >5% in absence of underlying reactive process

Tissue biopsy demonstrating replacement and distortion of normal tissue by plasma cells

More than 500 plasma cells/mm<sup>3</sup> in peripheral blood

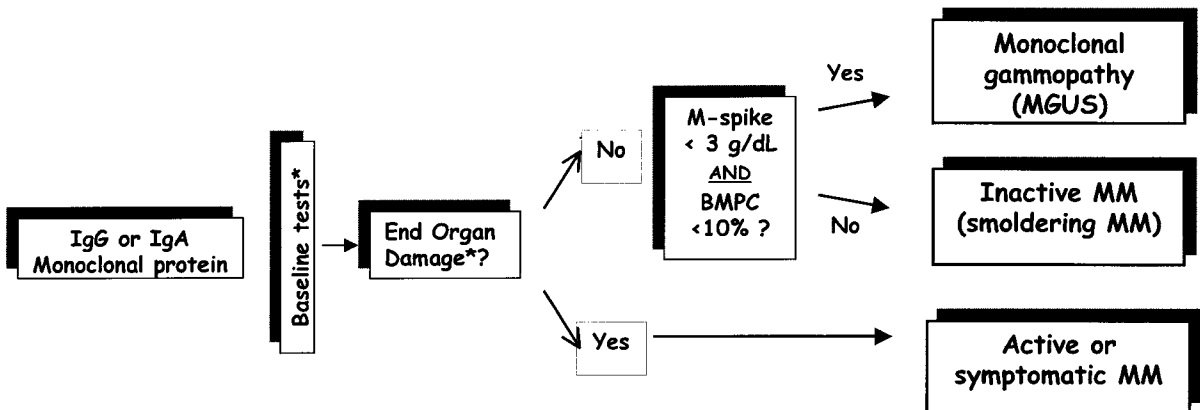
Osteolytic lesion unexplained by other causes

If M protein absent in serum and urine, there must be radiologic evidence of osteolytic lesions or palpable tumors and 1 or more of the following must be present:

Marrow plasmacytosis of >20% from 2 sites in absence of reactive process

Tissue biopsy demonstrating replacement and distortion of normal tissue by plasma cells

Data from Committee of the Chronic Leukemia-Myeloma Task Force, National Cancer Institute (1973).



\* End organ damage without other explanation

- Bone marrow: hemoglobin, more than 2 g/dl below normal
- Bones:
  - Lytic lesions or osteoporosis with compression fracture
  - Serum calcium, more than 1 mg/dl above normal
- Kidneys: serum creatinine, more than 1 mg/dl above normal

**Fig. 3.7.** Diagnostic criteria. *BMPC*, bone marrow plasma cells; *MGUS*, monoclonal gammopathy of undetermined significance; *MM*, multiple myeloma. Personal communication from Dr. R. A. Kyle



perience of treating and studying multiple myeloma patients. Because multiple myeloma includes a spectrum of biologic and clinical features, treatment should not commence based on a single threshold value. The diagnosis of active myeloma is not a straightforward pathologic one; rather, it is a clinical diagnosis that requires thoughtful synthesis of multiple variables. Those patients with Durie-Salmon stage I disease, who also meet the criteria for inactive, smoldering, or asymptomatic myeloma, should be managed expectantly. Median progression-free survival in asymptomatic stage I patients, observed without any therapy, is 12 to more than 48 months (Facon et al. 1995; Hjorth et al. 1993; Peest et al. 1995; Riccardi et al. 2000); for similar stage II patients, progression-free survival is 12 months (Peest et al. 1995). No survival advantage has been demonstrated by treating asymptomatic myeloma patients (Alexanian 1980; Hjorth et al. 1993; Riccardi et al. 2000).

### 3.7 Differential Diagnosis

The diagnosis of multiple myeloma is made from a constellation of findings, including anemia, monoclonal proteins, bone lesions, renal complications, hypercalcemia, and bone marrow plasmacytosis. Often the diagnosis is straightforward, but other disease entities associated with hypergammaglobulinemia or monoclonal bone marrow plasma cells must also be considered. These include reactive plasmacytosis, MGUS, primary systemic amyloidosis, Waldenström macroglobulinemia, light chain deposition disease, Fanconi syndrome,

**Table 3.3. Differential diagnosis of multiple myeloma**

Reactive plasmacytosis and polyclonal hypergammaglobulinemia
Monoclonal gammopathy of undetermined significance
Primary systemic amyloidosis
Plasma cell leukemia
POEMS syndrome (osteosclerotic myeloma)
Solitary plasmacytoma
Waldenström macroglobulinemia
Light chain deposition disease
Acquired Fanconi syndrome

**Table 3.4. Criteria for diagnosis of MGUS, SMM, and MM according to Kyle and Greipp**

MGUS <sup>a</sup>
Serum monoclonal protein (<3 g/dL)
No anemia, renal failure, or hypercalcemia
Bone lesions absent on radiographic bone survey <sup>b</sup>
Bone marrow <10% plasma cells
SMM <sup>a</sup>
Serum monoclonal protein (≥3 g/dL) and/or ≥10% marrow plasma cells or aggregates on biopsy
No anemia, renal failure, or hypercalcemia attributable to myeloma
MM
Monoclonal protein present in serum or urine
≥10% marrow plasma cells on biopsy or histologic evidence of plasmacytoma
Plus one or more of the following
Anemia
Lytic lesions or osteoporosis and ≥30% plasma cells in marrow
Bone marrow plasma cell labeling index >1%
Renal insufficiency
Hypercalcemia

MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma.

<sup>a</sup> Patients with MGUS and SMM must not have solitary plasmacytoma, amyloidosis, or light-chain deposition disease.

<sup>b</sup> Computed tomography or magnetic resonance imaging may be needed to rule out skeletal lesions.

Data from Kyle and Greipp (1980).

solitary plasmacytoma, osteosclerotic myeloma or POEMS syndrome, and plasma cell leukemia (Table 3.3).

#### 3.7.1 Reactive Plasmacytosis and Polyclonal Hypergammaglobulinemia

Reactive plasmacytosis and polyclonal hypergammaglobulinemia must be distinguished from a clonal process. Patients with liver disease, chronic infections including human immunodeficiency virus, connective tissue diseases, other lymphoproliferative disorders, and carcinoma can have increased bone marrow plasmacy-

tosis (polyclonal) and hypergammaglobulinemia (polyclonal). These conditions should not be confused with multiple myeloma or MGUS, which are clonal processes.

### 3.7.2 MGUS

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Two percent of patients older than age 50 years have MGUS, which is a benign counterpart or precursor lesion of multiple myeloma (Kyle et al. 2002). It is characterized by an M protein in the serum or urine, without evidence of multiple myeloma or other serious gammopathy-related disorder. MGUS patients do not have bone marrow suppression, lytic bone lesions, hypercalcemia, renal failure, or increased susceptibility to infection. Standard clinical features do not accurately predict which patients will remain stable, and multiple myeloma develops in approximately 1% of MGUS patients per year. The clinical distinction between MGUS and asymptomatic multiple myeloma has been derived from an arbitrary definition (Table 3.4 and Fig. 3.7), although the underlying biologic conditions should prove to be distinct.

The greatest challenges in differentiating MGUS from myeloma occur in patients who have MGUS and 1) senile osteoporosis, 2) renal insufficiency from another cause, or 3) hypercalcemia due to hyperparathyroidism. Approximately 50% of women older than age 60 years have osteoporosis, and a fraction of these even have a vertebral compression fracture. Computed tomographic scan of the spine may help distinguish between senile osteoporosis and myelomatous bone disease. Similarly, renal insufficiency due to long-standing diabetes, hypertension, or nonsteroidal drug use is not uncommon. In such cases, a patient may still have MGUS (or asymptomatic myeloma, for that matter) and “end-organ damage.” The key is whether the damage is attributable to the plasmaproliferative disorder or another cause. In some instances, renal biopsy may be required to clarify this issue.

### 3.7.3 Primary Systemic Amyloidosis

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Primary systemic amyloidosis is a rare disorder that is characterized by the deposition of amyloid fibrils. These fibrils are composed of immunoglobulin light chain fragments in a  $\beta$ -pleated sheet conformation. It should be suspected when a patient with a monoclonal protein in the serum or urine presents with nephrotic-range

proteinuria (primarily albumin) with or without renal insufficiency, cardiomyopathy, hepatomegaly, or peripheral neuropathy. Patients usually present with weight loss or fatigue. Anemia is rare at presentation. Symptoms related to the affected organ are also seen. Median percentage of clonal plasma cells in these patients is only 5%. A histologic diagnosis is made by demonstrating the amyloid fibrils – green birefringence under polarized light by using a Congo red stain or 8- to 10-nm nonbranching fibrils by electron microscopy. Nearly 90% of patients with amyloid have a bone marrow or fat aspirate specimen positive for amyloid. In the remaining 10%, a biopsy specimen of the affected organ is positive.

### 3.7.4 Waldenström Macroglobulinemia

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Waldenström macroglobulinemia should not be confused with IgM myeloma, which comprises only about 1% of myeloma cases (Kyle et al. 2003). Patients with Waldenström macroglobulinemia may have anemia, hyperviscosity, B symptoms, bleeding, and neurologic symptoms. Significant lymphadenopathy or splenomegaly may also be present. Lytic bone disease would be exceptional; if present, IgM myeloma should be considered. In Waldenström macroglobulinemia, bone marrow biopsy typically reveals infiltration with clonal lymphoplasmacytic cells which are CD20 positive. The natural history and treatment options for Waldenström macroglobulinemia are different from those of multiple myeloma.

### 3.7.5 Light Chain Deposition Disease

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The nonamyloidogenic light chain deposition diseases (LCDD) are due to pathologic protein deposition in various tissues and organs. Unlike the light chain deposits observed in patients with primary systemic amyloidosis, these infiltrates are not congophilic by light microscopy, and by electron microscopy nonbranching fibrils are not observed. Instead, amorphous nodular deposits are observed.

LCDD may occur with or without coexistent multiple myeloma. Renal involvement is most common, followed distantly by cardiac and hepatic. Clinically, LCDD can be differentiated from multiple myeloma and primary systemic amyloidosis by the following findings.

As in primary systemic amyloidosis, early in the disease course the light chain deposits have a predilection for the renal glomeruli rather than the tubules. This results in nonselective proteinuria, that is, a predominance of albuminuria, which is not usual in multiple myeloma. It is impossible clinically to distinguish the nephropathy, cardiomyopathy, or hepatopathy from primary systemic amyloidosis without tissue biopsy. The underlying clone is more commonly monoclonal  $\kappa$  than  $\lambda$  in LCDD.

The prognosis of patients who have this disorder depends on whether there is underlying multiple myeloma. In one retrospective study of 19 patients with LCDD, 5-year actuarial patient survival and survival free of end-stage renal disease were 70% and 37%, respectively.

### 3.7.6 Acquired Fanconi Syndrome

Fanconi syndrome is a rare complication of plasma cell dyscrasias characterized by diffuse failure in reabsorption at the level of the proximal renal tubule and resulting in glycosuria, generalized aminoaciduria, and hypophosphatemia. Acquired Fanconi syndrome is usually associated with MGUS. Overt hematologic malignancies may occur, such as multiple myeloma, Waldenström macroglobulinemia, or other lymphoproliferative disorders. The prognosis for survival is good in the absence of overt malignant disease. Clinical manifestations include slowly progressive renal failure and bone pain due to osteomalacia. The diagnosis of Fanconi syndrome can be made when a patient with a monoclonal plasma cell disorder presents with hypophosphatemia, hypouricemia, aminoaciduria, phosphaturia, and glycosuria. Bence Jones proteinuria is usually present and is almost always of the  $\kappa$  type. Rare patients have been reported with Fanconi syndrome associated with  $\lambda$  Bence Jones proteinuria.

Treatment consists of supplementation with phosphorus, calcium, and vitamin D. Chemotherapy may benefit patients with rapidly progressive renal failure or symptomatic malignancy.

### 3.7.7 POEMS Syndrome (Osteosclerotic Myeloma)

Osteosclerotic myeloma is a rare variant of myeloma ( $\leq 3.3\%$  of cases). There is a straight osteosclerotic vari-

ant that is similar to multiple myeloma in that anemia, significant bone marrow plasmacytosis, hypercalcemia, and renal insufficiency occur. Survival in these patients is comparable to that of classic multiple myeloma patients. There is, however, a more interesting form, which is known as Crow-Fukase syndrome, Takatsuki syndrome, and POEMS syndrome (*polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes*) (Dispenzieri et al. 2003). This variant is associated with multiple paraneoplastic phenomena, and its natural history is not similar to that of classic multiple myeloma. The acronym POEMS captures several of the dominant features of the syndrome, but it omits the sclerotic bone lesions, Castleman disease, papilledema, peripheral edema, ascites, polycythemia, thrombocytosis, fatigue, and clubbing commonly observed in the disorder. Not all features are required to make the diagnosis; at a minimum, however, a patient must have: 1) peripheral neuropathy, 2) osteosclerotic myeloma (i.e., a clonal plasma cell dyscrasia and at least 1 sclerotic bone lesion) or Castleman disease, and 3) at least 1 of the other features mentioned. The peak incidence of POEMS syndrome is in the 5th and 6th decades of life, and there is a male predominance.

Although the precise mechanism of POEMS syndrome is unknown, VEGF appears to be a driving factor in this disorder. Despite the presence of osteosclerotic bone lesions that microscopically contain clonal plasma cell infiltrates, bone marrow aspirate and biopsy of the iliac crest typically yield only about 5% monoclonal lambda plasma cells.

Treatment for this disorder is not standardized. For an isolated plasmacytoma, external beam irradiation is the preferred first-line treatment. It produces substantial improvement of the neuropathy in more than half of the patients who have a single lesion or multiple lesions in a limited area. If there are widespread lesions, chemotherapy and, potentially, peripheral blood stem cell transplantation should be considered. Responses of systemic symptoms and skin changes tend to precede those of the neuropathy, with the former beginning to respond within a month and the latter within 3 to 6 months. The most common causes of death are cardiorespiratory failure, progressive inanition, infection, capillary leak-like syndrome, and renal failure. The neuropathy may be unrelenting and contribute to progressive inanition and eventual cardiorespiratory failure and pneumonia. Patients do not die of classic myeloma (ie, progressive bone marrow failure or hypercalcemia).

### 3.8 Treatment for Multiple Myeloma

Before starting therapy for multiple myeloma, a distinction must be made between inactive (smoldering, indolent, asymptomatic) myeloma and active myeloma, which requires therapy (Fig. 3.7) (International Myeloma Working Group, 2003). Approximately 20% of patients with multiple myeloma are recognized by chance without significant symptoms; such patients can be carefully monitored without instituting therapy. Risk factors for progression include serum M protein  $>3$  g/dL, IgA isotype, and Bence Jones protein excretion  $>50$  mg per day. Patients with 2 or more of these features required treatment at a median of 17 months, whereas the absence of any adverse variable was associated with prolonged stability (median, 95 months) ( $P < 0.01$ ) (Weber et al. 1997). Patients with one or more lytic bone lesions or circulating plasma cells on peripheral blood labeling index are also at higher risk for early progression.

Once the decision has been made to institute therapy for symptomatic disease, a long-term plan for managing the disease should be formulated before instituting therapy. Figure 3.8 outlines a possible treatment algorithm. Because high-dose therapy with hematopoietic stem cell support has been accepted as an important treatment modality for patients younger than age 65 years, alkylator-based therapy should be avoided before hematopoietic stem cell collection in patients considered candidates for high-dose therapy.

#### 3.8.1 Systemic Therapy

##### 3.8.1.1 General Comments

Historically, the bifunctional alkylating agents, like melphalan and cyclophosphamide, have been the foundation of standard therapy for multiple myeloma (Fig. 3.1). Myeloma cells tend to be slowly proliferating,

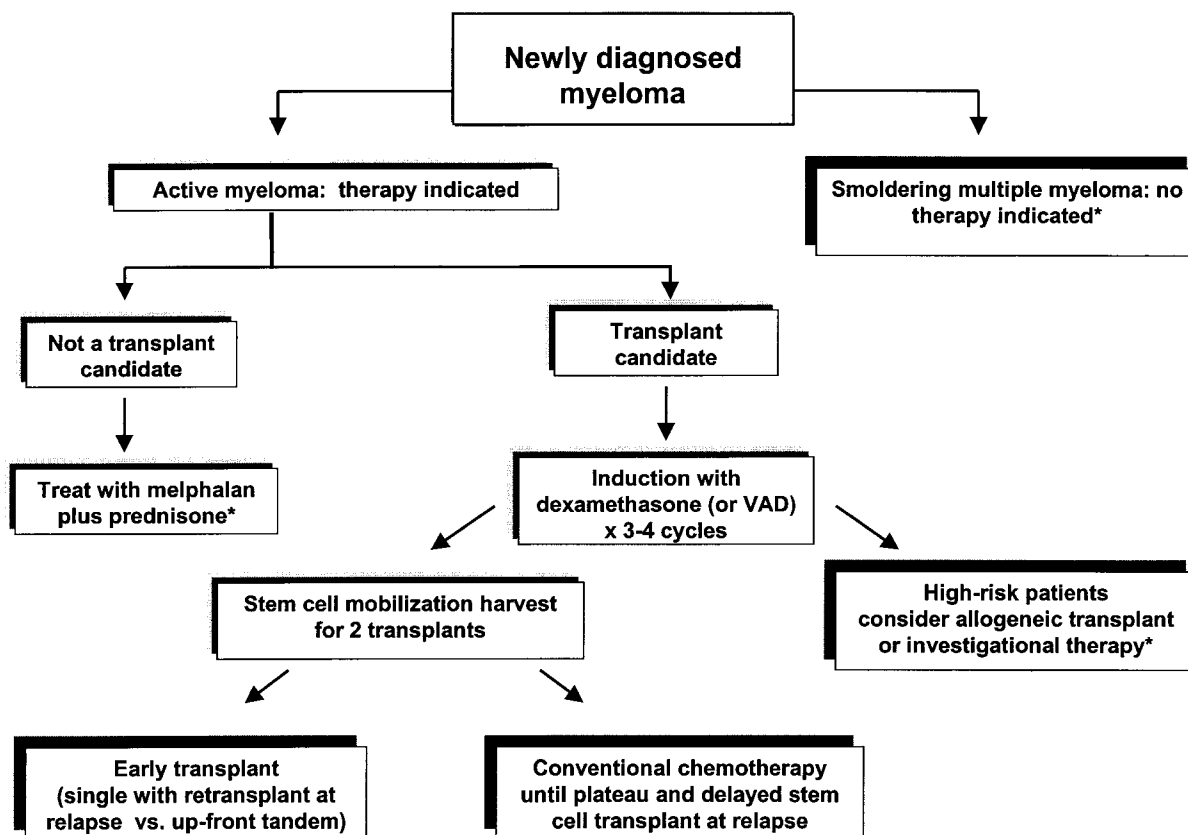
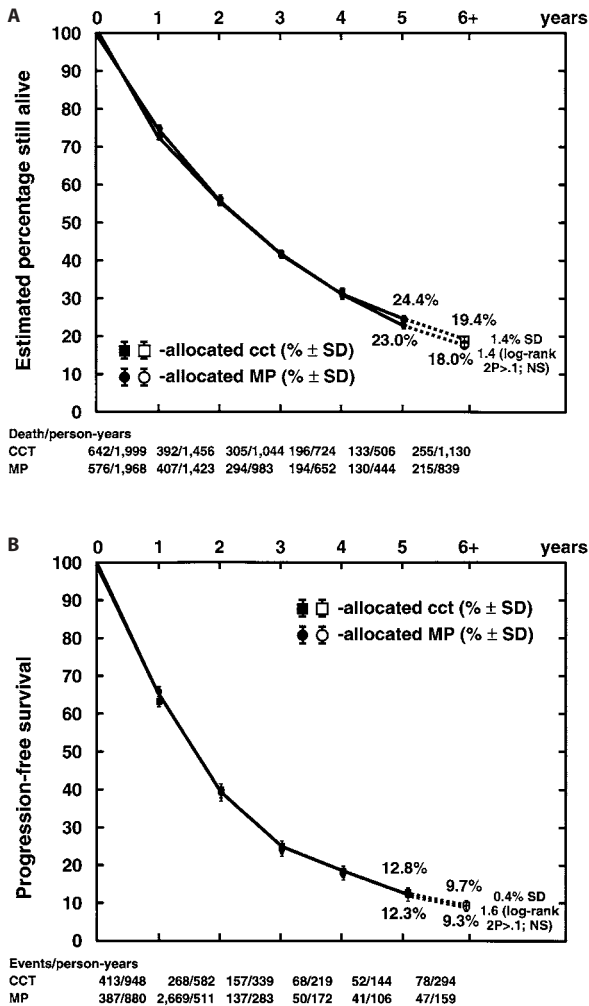


Fig. 3.8. Possible treatment algorithm. \*At any point in the disease, consider clinical trial or investigational therapy directed at particular phase of disease. VAD, vincristine, doxorubicin, and dexamethasone



**Fig. 3.9.** Melphalan and prednisone (MP) versus combined chemotherapy (cct) as induction. Results from 6,633 patients from 27 randomized trials. *A*, Overall survival. *B*, Response duration. (From the Myeloma Trialists' Collaborative Group [1998]. By permission of the American Society of Clinical Oncology.)

and alkylators, which do not rely heavily on cell division and DNA replication, are useful. Before the recognition of thalidomide's activity in myeloma, the bifunctional alkylators, nitrosoureas, doxorubicin, and glucocorticoids were the primary agents shown to have single agent activity against multiple myeloma in vivo. These drugs and vincristine, either singly or in combination, have been the mainstay of chemotherapy for myeloma from the early 1960s to the present. Even though vincristine has not been shown to have significant single agent in vivo activity or to clearly improve overall sur-

vival (MacLennan et al. 1992; Tribalto et al. 1985), it is included in multiple therapeutic regimens. Decades of study suggest that although response rates are higher with regimens that combine multiple active agents as part of initial therapy, these regimens do not improve overall survival rates (Myeloma Trialists' Collaborative Group 1998).

Interferon- $\alpha$  has been incorporated into both induction and maintenance protocols with modest benefit since the 1980s because of its single agent activity (Myeloma Trialists' Collaborative Group 2001). Both autologous and allogeneic stem cell transplantation have received considerable attention since McElwain and Powles' description in 1983 of the benefit of dose intensification of melphalan in patients with multiple myeloma. With the recognition of thalidomide as a new agent with activity against multiple myeloma in 1999 and exciting new agents like the IMiDs and proteasome inhibitors, there is hope that the next 4 decades of myeloma treatment will be even more promising than the last (Fig. 3.1).

Before discussing induction (Fig. 3.9), transplantation, maintenance, and salvage therapies, 2 general concepts will be reviewed: interpretation of study response data and the efficacy of single chemotherapeutic agents commonly used to treat myeloma. Table 3.5 serves as a reference for commonly cited regimens.

### 3.8.1.2 Interpreting Study Response and Survival Data

Four points are emphasized regarding the interpretation and comparisons of the myeloma treatment literature. First, definitions of response vary. Second, definitions of evaluable patients may be different. Third, concurrent corticosteroid therapy, either as part of the regimen or for other indications, may confound interpretation of efficacy. Finally, patient population risk and prognosis may differ substantially. Lead-time bias and inappropriate incorporation of patients with MGUS or inactive myeloma can significantly distort survival estimates, as can effective salvage regimens.

The measurement of myeloma disease burden, and therefore response, is complex, and different investigators have used different methods to determine response (Table 3.6). The 4 most common response criteria are those of the Chronic Leukemia-Myeloma Task Force (CLMTF) (1973), Southwest Oncology Group (SWOG)

**Table 3.5.** Commonly cited regimens and their dosage schedules

Drug regimen	VCR	Mel	CTX	BCNU	ADR	Glucoc
MP	–	9 mg/m <sup>2</sup> per d d 1–4 q 4 wk or 0.15 mg/kg per d d 1–7 q 6 wk	–	–	–	Pred 100 mg/d d 1–4 q 4 wk or Pred 60 mg/d d 1–7 q wk
CP <sup>a</sup>	–	–	250 mg/m <sup>2</sup> per d d 1–4 or 1,000 mg/m <sup>2</sup> IV	–	–	Pred 100 mg/d d 1–4 or Pred 50 mg qod
VMCP <sup>b</sup>	1 mg d 1	6 mg/m <sup>2</sup> per d d 1–4	125 mg/m <sup>2</sup> per d d 1–4	–	–	Pred 60 mg/m <sup>2</sup> per d d 1–4
VBAP <sup>b</sup>	1 mg d 1	–	–	30 mg/m <sup>2</sup> IV d 1	30 mg/m <sup>2</sup> IV d 1	Pred 60 mg/m <sup>2</sup> per d d 1–4
ABCM <sup>c</sup> (MacLennan et al. 1992)	–	6 mg/m <sup>2</sup> per d d 1–4	100 mg/m <sup>2</sup> per d d 1–4	30 mg/m <sup>2</sup> IV d 1	30 mg/m <sup>2</sup> IV d 1	–
M-2 (Case et al. 1977 <sup>d</sup> ) (ECOG modification)	0.03 mg/kg IV d 1	0.25 mg/kg d 1–7	10 mg/kg IV d 1	0.5 mg/kg IV d 1	–	Pred 1 mg/kg d 1–7
MOCCA <sup>d</sup>	0.03 mg/kg IV d 1	0.25 mg/kg d 1–7	10 mg/kg IV d 1	CCNU 40 mg po d 1	–	0.8 mg/kg po d 1–7
VAD <sup>d</sup> (Barlogie et al. 1984)	0.2 mg/m <sup>2</sup> per d d 1–4 CI	–	–	–	9 mg/m <sup>2</sup> per d d 1–4 CI	Dex 40 mg/d d 1–4, 9–12, 17–20
VAMP* (Forgeson et al. 1988)	0.4 mg/d CI d 1–4	–	–	–	9 mg/m <sup>2</sup> per d CI	Methylpred 1 g/m <sup>2</sup> per d d 1–4

ABCM, VBAP/VMCP without vincristine or prednisone; ADR, doxorubicin (Adriamycin); BCNU, carmustine; CI, continuous infusion; CP, cyclophosphamide and prednisone; CTX, cyclophosphamide; d, day; glucoc, corticosteroid; IV, intravenous; Mel, melphalan; MOCCA, VBMCP with CCNU replacing BCNU; M-2, VBMCP; MP, melphalan and prednisone; po, by mouth; q, every; qod, every other day; VAD, vincristine, doxorubicin, and dexamethasone; VAMP, vincristine, doxorubicin, and methylprednisolone; VBAP, vincristine, BCNU, doxorubicin, and prednisone; VCR, vincristine; VMCP, vincristine, melphalan, cyclophosphamide, and prednisone; wk, week.

<sup>a</sup> Repeated at 4- or 5-week intervals.

<sup>b</sup> VMCP and VBAP are commonly alternating every 3 weeks.

<sup>c</sup> AB and CM portions of regimen are given alternating every 3 weeks.

<sup>d</sup> Repeated every 5 weeks.

(1975), Eastern Cooperative Oncology Group (ECOG) (Oken et al. 1996a), and IBMTR/ABMTR (Bladé et al. 1998). Although all take into account hemoglobin, calcium, bone changes, and bone marrow plasmacytosis, the main distinction among them is their consideration

of the serum and urine M components. With the exception of the old SWOG criteria (McLaughlin and Alexanian 1982), a partial response has been considered to be a 50% reduction in serum M component and a >50% to 90% reduction in urine M component. In the



Table 3.6. Response criteria					
Response	Study	% BMPC	M protein		Duration, wk
			Serum	Urine	
Complete response	CLMTF (Chronic Leukemia-Myeloma Task Force 1973)	< 1 <sup>a</sup>	Not defined		8
	SWOG (McLaughlin and Alexanian 1982)		IF –	IF –	
	IBMTR <sup>b</sup> (Bladé et al. 1998)		IF –	IF –	
Objective response Improvement	SWOG	< 5	↓ ≥ 75% <sup>c</sup>	↓ ≥ 90%	8
	SWOG		↓ ≥ 50% <sup>c</sup>	↓ ≥ 75%	8
	CLMTF <sup>d</sup>		↓ ≥ 50%	↓ ≥ 50% <sup>e</sup>	–
	ECOG		↓ ≥ 50%	↓ ≥ 90%	6
	IBMTR		↓ ≥ 50%	↓ ≥ 90% <sup>f</sup>	6
Stable, no change, or no response	SWOG	–	< ± 25% <sup>c</sup>	< ± 25%	–
	ECOG		Not CR, NCR, or PR		–
	IBMTR		Neither MR nor progression		–
Plateau	ECOG	–	< ± 20%	< ± 20%	4
	IBMTR		< ± 25%	< ± 25%	12
Progression	SWOG	> 25 <sup>i</sup>	> 25% <sup>c</sup>	> 25%	–
	ECOG		≥ 50% <sup>g</sup>	≥ 50% <sup>h</sup>	–
	IBMTR		> 25% <sup>j</sup>	> 25% <sup>h</sup>	–

Other special categories include:

ECOG NCR, which includes < 5% BMPC or CR by serum and urine but no confirmatory BM performed.

SWOG VGPR, which includes < 5% BMPC, ≥ 90% reduction of serum M protein and ≤ 100 mg of urinary light chain excretion.

IBMTR/ABMTR MR, which includes 25% to 49% reduction of serum M protein and 50% to 89% reduction of 24-hour urinary light chain excretion, which still exceeds 200 mg per 24 hours.

BMPC, bone marrow plasma cells; CLMTF, Chronic Leukemia-Myeloma Task Force; CR, complete response; ECOG, Eastern Cooperative Oncology Group; IBMTR, International Blood and Bone Marrow Transplant Registry; IF, immunofixation; MR, minimum response; NCR, near complete response; PR, partial response; SWOG, Southwest Oncology Group.

<sup>a</sup> Clonal plasma cells as measured by cytoplasmic immunoglobulin flow cytometry.

<sup>b</sup> Makes allowance for nonsecretory myeloma and plasmacytomas.

<sup>c</sup> Change in synthetic index and not monoclonal protein concentration.

<sup>d</sup> Response also takes into account reduction in size of plasmacytomas, > 2 g/dL Hb rise, weight gain, correction of calcium, renal function, albumin.

<sup>e</sup> If pretreatment value greater than 1 g/24 hours, then decrease to 50% or less of pretreatment value; if pretreatment value 0.5 to 1 g/24 hours, then decrease to less than 0.1 g/24 hours; otherwise, if pretreatment value less than 0.5 g/24 hours, variable should not be used to measure response.

<sup>f</sup> Or < 200 mg/24 hours.

<sup>g</sup> Absolute increase must be at least 2 g/dL.

<sup>h</sup> Absolute increase must be greater than 200 mg/24 hours.

<sup>i</sup> Absolute increase must be at least 10%.

<sup>j</sup> Absolute increase must be greater than 0.5 g/dL.

earliest literature, response included such factors as increasing hemoglobin concentration or performance status, or decreasing blood urea nitrogen. Some authors have included a minimal response (25% to 49% reduction in serum M protein) as a response. Neither the CLMTF or SWOG originally had a complete response category, because it was unusual for the M protein to disappear completely. It was not until the advent of high-dose melphalan that investigators like Selby et al. (1987) began to define a complete remission category. Their definition, unlike more modern definitions, only included disappearance of M protein by electrophoresis, which is less sensitive than immunoelectrophoresis or immunofixation. Subsequent definitions have required immunofixation negativity to qualify as complete remission (Bladé et al. 1998). Up until about 1990, an SWOG objective response was a 75% reduction in the *tumor mass index* and an improvement was a 50% to 74% reduction in the tumor mass index (McLaughlin and Alexanian 1982).

The early Medical Research Council Myelomatosis trial evaluated the efficacy of treatment, not by the degree of paraprotein reduction but by the proportion of patients achieving plateau (MacLennan et al. 1992). There has been a new iteration of the SWOG response criteria over the last decade, and the M component (rather than the tumor mass index) is used as the primary measurement of the plasma cell burden. Currently, the serum and urine protein response groups include: 1) a partial response is a 50% reduction in the serum and urine M components, 2) a remission is a 75% reduction in the serum and a 90% reduction in the urine M components, and 3) a complete remission is total absence of any monoclonal protein by immunofixation of the serum or urine (personal communication with John Crowley). At Mayo, we have adopted the IBMTR/ABMTR criteria, and we incorporated the IFM's very good partial response category.

The roving denominator also creates challenges in interpreting therapeutic studies. Often an intention to treat analysis is not used to describe response rates or survival, which artificially inflates these end points. Definitions of evaluable patients may often include only those patients who received an adequate trial (3 or 6 months) of therapy, thereby excluding patients with early deaths or progression. In addition, in a steroid-responsive tumor like myeloma, coincident use of prednisone or dexamethasone as an antiemetic or therapy for hypercalcemia may seriously confound the results. Fi-

nally, the striking heterogeneity of prognosis in myeloma patients cannot be excluded as a major confounding factor in interpreting both phase 2 and 3 trials. Several prognostic indicators have been identified, including stage,  $\beta_2$ M, labeling index, renal function, and chromosomal abnormalities. Unfortunately, their predictive value is limited, only skimming the surface of myeloma biology and prognosis.

### 3.8.1.3 Efficacy of Single Chemotherapeutic Agents

#### 3.8.1.3.1 Single Agent Efficacy of Melphalan

Bergsagel et al. demonstrated the benefit of melphalan in 14 of 24 patients with multiple myeloma. Others (Table 3.7) have substantiated that melphalan as a single agent results in response rates of 20% to 34% and median overall survival duration of 15 to 27 months (Bergsagel et al. 1967; MacLennan et al. 1992; Rivers and Patno 1969; Sporn and McIntyre 1986).

#### 3.8.1.3.2 Single Agent Efficacy of Cyclophosphamide

Korst et al. (Kyle 2000; Sporn and McIntyre 1986) were the first to report on the activity of oral cyclophosphamide. Twenty-four percent of multiple myeloma patients achieved a partial response (50% M-protein reduction), and 48% had objective improvement, that is, an improvement in the peripheral blood values, bone marrow findings, or serum blood urea nitrogen. Median survival was 24.5 months in all 207 patients and 32 months in the group that received at least 2 months of cyclophosphamide therapy. The single agent activity of cyclophosphamide has been demonstrated in a placebo-controlled trial (Rivers and Patno 1969) and in multiple studies in untreated patients (Medical Research Council's Working Party on Leukaemia in Adults 1980; Sporn and McIntyre 1986) and in those who relapsed or are refractory (Lenhard et al. 1994).

#### 3.8.1.3.3 Single Agent Efficacy of Glucocorticoids

In 1950, Thorn et al. reported the first observations on the beneficial effects of adrenocorticotrophic hormone on myeloma. During that decade, it was recognized that adrenocorticotrophic hormone, cortisone, and prednisone decreased bone pain, improved hypercalcemia, increased hemoglobin values, and decreased abnormal serum and urine globulin concentrations. Subsequently,

Table 3.7. Early (1969 to 1982) randomized trials – untreated myeloma					
Study	Agent	Schedule	N	RR, %	Overall survival, mo
Rivers and Patno, 1969	CTX	2–4 mg/kg per d	54	21	11.5 <sup>a</sup>
	Placebo				3.5
Rivers and Patno, 1969	CTX	4 mg/kg per d	49	28	13
	M	0.1 mg/kg per d	54	34	15.5
Alexanian et al., 1969	M qd	0.025 mg/kg per d	35	17	18
	M intermittent	0.25 mg/kg d 1–4	69	32	18
	M alt. P	0.25 mg/kg d 1–4 & 1 mg/kg MWF	28	61	24
	M concurr. P	0.25 mg/kg d 1–4 & 2 mg/kg d 1–4	51	65	17
Medical Research Council's Working Party on Leukaemia in Adults, 1971	CTX	150 mg/d	114	NG	28 <sup>b</sup>
	M	4 mg/d	105	NG	24 <sup>b</sup>
Costa et al. 1973	M qd	0.15 mg/kg x 7, maintenance 0.05 kg per d	53	20	27 (30, 21) <sup>c</sup>
	M qd & P	M: as above & P: 1.25 mg/kg per d with taper 8 wk	70	39	NG (53, 9)
	M qd, P, & testosterone	M & P: as above & testosterone; 10 g/kg per wk	56	43	NG (36, 4)
Medical Research Council's Working Party on Leukaemia in Adults, 1980	MP	M: 10 mg/d d 1–7; P: 40 mg/d d 1–7 q 3 wk	174	NG	32 <sup>b,d</sup>
	CTX IV	600 mg/m <sup>2</sup> q 3 wk	179	179	24
	MP	See above	71	NG	6 <sup>b,e</sup>
	CMLP	C: 250 mg/m <sup>2</sup> po d 1–3; M: 5 mg/m <sup>2</sup> d 1–3; L: 50 mg/m <sup>2</sup> d 4; & P: 40 mg/m <sup>2</sup> d 1–3 q 4 wk	61	NG	6

Table continues on page 76.

high-dose corticosteroids (Table 3.6) have been shown to produce response rates of 40% to 50% and ~25% in previously untreated and refractory or relapsed patients, respectively (Alexanian et al. 1992; Gertz et al. 1995; Sporn and McIntyre 1986). Despite their contribution to quicker and more abundant responses, the data

are conflicting as to whether corticosteroids prolong survival (Sporn and McIntyre 1986). The mechanism of action of this drug class is complex. Corticosteroids suppress the production of cytokines important in myeloma growth, like IL-6 and IL-1 $\beta$ , and reduce nuclear factor  $\kappa$ B activity, resulting in enhanced apoptosis.

**Table 3.7** (continued)

Study	Agent	Schedule	N	RR, %	Overall survival, mo
Cornwell et al., 1988	MP	M: 0.15 mg/kg d 1–7; P: 0.8 mg/kg with taper	100	44 <sup>f</sup>	27
	Carmustine	Carmustine: 150 mg/m <sup>2</sup> IV; P: 0.8 mg/kg with taper	124	34	21
	Lomustine	Lomustine: 100 mg/m <sup>2</sup> qd; P: 0.8 mg/kg with taper	137	30	21

Alt, alternating; concurr., concurrently; CTX, cyclophosphamide; IV, intravenous; L, lomustine; M, melphalan; NG, not given; P, prednisone; po, by mouth; qd, daily.

<sup>a</sup> Overall survival is significant at  $P=0.03$ . No corticosteroids allowed in trial.

<sup>b</sup> Survival estimated from survival curves.

<sup>c</sup> Patients stratified for good and poor risk; median survival given as all patients (good risk, poor risk). Authors note that much quicker response observed with prednisone but worse survival with prednisone in poor-risk patients.

<sup>d</sup> Patients were required to have BUN  $\leq 10$  mM. Difference not significant ( $P=0.16$ ).

<sup>e</sup> All patients had BUN  $>10$  mM.

<sup>f</sup> Response rate between melphalan and lomustine arms significant. Median survival is not different.

#### 3.8.1.3.4 Single Agent Efficacy of Vincristine

Alexanian et al. (1977) suggested that regimens that included vincristine resulted in better patient outcome than protocols not including this agent. The theory behind its posited utility was that after an initial kill by alkylating agents, the observed subsequent increase in mitotic index made myeloma cells more sensitive to vincristine. The report by Case et al. (1977) has been cited as confirmatory evidence for activity of vincristine in myeloma. However, several randomized controlled trials do not support this premise (Sporn and McIntyre 1986; Tribalto et al. 1985). The most compelling of these is the MRC IV Trial in Myelomatosis, which randomized 530 newly diagnosed myeloma patients to monthly melphalan and prednisone, with or without monthly vincristine. Median survival in both arms was 26 months (MacLennan et al. 1992). Although never evaluated as a single agent in newly diagnosed myeloma, vincristine has little activity as a single agent in refractory disease. Twenty-one patients were treated with 0.5 mg bolus followed by 0.25 to 0.5 mg/m<sup>2</sup> per day as a continuous infusion over 5 days on a 3-week schedule. Two patients had transient responses (1.2 and 2.2 months). Finally, the activity credited to vincristine as a maintenance therapy is also ambiguous.

#### 3.8.1.3.5 Single Agent Efficacy of Anthracyclines

Doxorubicin is the most commonly used anthracycline in the treatment of myeloma, but it has not been studied as a single agent in newly diagnosed myeloma patients. Its activity as a single agent in relapsed or refractory disease is modest, with response rates of about 10% (Alberts et al. 1976). A phase 2 trial of mitoxantrone as a single agent yielded a partial response rate of 3% (1 of 35 patients). An additional 4 patients showed clinical improvement lasting 4 to 7 months. Idarubicin is another anthracycline that has been studied in the context of multiple myeloma. Response rates of 0% to 27% have been observed in relapsed and refractory patients with single agent oral regimens.

#### 3.8.1.3.6 Single Agent Efficacy of Etoposide

In relapsed and refractory disease, single agent etoposide has minimal activity; in 85 patients the response rate was  $<5\%$ . However, Barlogie et al. (1989) treated 14 patients with 200 mg/m<sup>2</sup> by continuous infusion, and 2 responded. In addition, there are 2 anecdotal reports of activity of low-dose oral etoposide.

### 3.8.1.3.7 Single Agent Efficacy of Nitrosoureas

The nitrosoureas have single agent activity in myeloma. In a randomized trial of 361 previously untreated patients (Table 3.7), objective response frequency with carmustine (BCNU) (40%) and lomustine (CCNU) (42%) was lower than that of melphalan (59%), although the survivals for all groups were not significantly different (Sporn and McIntyre 1986).

### 3.8.1.3.8 Single Agent Efficacy of Interferon

Since the original report by Mellstedt et al. of activity of human leukocyte interferon in patients with myeloma, multiple studies have confirmed the findings with daily human leukocyte interferon (3–9 MU/day) and with recombinant interferon- $\alpha$ . Although the earliest studies suggested response rates of up to 60%, subsequent studies yielded rates of 15% to 20% (Myeloma Trialists' Collaborative Group 2001). Toxicity was not inconsequential. In vitro activity had good predictive value for in vivo clinical response in 26 patients studied. In vitro, interferon has a stimulatory effect in about one-third of patients' myeloma samples.

### 3.8.1.3.9 Single Agent Efficacy of Thalidomide

Recognition of the role of increased angiogenesis in the pathogenesis and progression of myeloma and evidence of thalidomide's antiangiogenic properties led to clinical trials in multiple myeloma. The observed responses in patients without high-grade angiogenesis suggest that thalidomide may act via other mechanisms. The actual antitumor mechanism is likely complex. In vitro data suggest that the drug and its metabolites may inhibit angiogenesis, modulate adhesion molecules of myeloma cells and their surrounding stroma, modulate cytokines, and affect natural killer cells. There is recent evidence that thalidomide and its analogs induce apoptosis and G<sub>1</sub> growth arrest in myeloma cells.

Multiple studies have confirmed the initial observation of Singhal et al. that thalidomide as a single agent in relapsed myeloma produces response rates in the range of 25% to 45%. Median response duration is 9 to 12 months, and 2-year progression-free survival is 10% to 20%. Thalidomide is now considered a standard therapy for multiple myeloma, although Food and Drug Administration approval for this indication is pending.

### 3.8.1.3.10 Single Agent Efficacy of Other Agents

Barlogie et al. (1989) explored the utility of cisplatin therapy for patients with myeloma. Fourteen patients were treated with 10 mg/m<sup>2</sup> for 7 days by continuous infusion, and 2 responded. The drug has been incorporated into other regimens for relapsed disease (Barlogie et al. 1989) and induction (Barlogie et al. 1999).

Cytosine arabinoside, teniposide, topotecan, deoxycorformycin, and paclitaxel have been reported to produce response rates of 7%, 28%, 16%, 0% to 15%, and 15% to 29%, respectively. Topotecan induces significant toxicity including  $\geq$  grade 3 granulocytopenia and thrombocytopenia in 93% and 53% of patients, respectively. Patients treated with paclitaxel were premedicated with 40 mg of dexamethasone every 21 days, bringing into question whether the observed responses were to dexamethasone or paclitaxel.

Agents that do not appear to have any activity in myeloma include drugs that are interesting from a historical perspective and drugs that have known activity in other diseases. Agents in the former category include diamidines like stilbamidine, 1-aminocyclopentanecarboxylic acid, amsacrine, aclarubicin, chlorozotocin, hexamethylmelamine, and azaserine. Other commonly used agents without activity against myeloma include methotrexate, 6-mercaptopurine, 6-thioguanine, 5-fluorouracil, fluorodeoxyuridine, hydroxyurea, mitomycin C, vinblastine, vindesine, carboplatin, bleomycin, ATRA (all trans-retinoic acid), fludarabine, and 2-chlorodeoxyadenosine. Although Durie et al. reported a 57% response rate with clarithromycin, subsequent reports did not verify this response rate, and the activity observed in the original report was attributed to concurrent corticosteroid therapy.

## 3.8.1.4 Induction Chemotherapy Regimens

### 3.8.1.4.1 Single Agent With or Without Corticosteroids for Induction

#### 3.8.1.4.1.1 Melphalan as Induction Therapy

Since early reports by Blokhin et al. and Bergsagel et al., various schedules of melphalan have been tried, including continuous daily dose, 6 to 10 mg/day for 2 to 3 weeks, followed by maintenance therapy of 0.01 to 0.03 mg/kg per day; intermittent total doses of 0.25 mg/day given for 4 days every 4 to 8 weeks; or 0.15 mg/kg per day for 7 days every 6 weeks. Several studies

suggest that the intermittent schedule is superior to continuous daily dosing (Sporn and McIntyre 1986).

The combination of melphalan and prednisone (Table 3.7) has been studied extensively. Response rates are 40% to 60% and anticipated median survivals are 18 to 42 months (Medical Research Council's Working Party on Leukaemia in Adults 1980; Myeloma Trialists' Collaborative Group 1998). Because of the variable gastrointestinal tract absorption of melphalan, intravenous regimens of 15 to 25 mg/m<sup>2</sup> every 4 weeks along with oral prednisone or dexamethasone have been tried and resulted in response rates of 50% to 82%.

Not until the report by McElwain and Powles (1983) on the successful use of high-dose melphalan (140 mg/m<sup>2</sup> intravenously) had dose intensity been studied in myeloma. In previously untreated patients, Selby et al. (1987) confirmed a 78% response rate, including 27% of patients whose M component was no longer visible by protein electrophoresis. This dose intensity without stem cell salvage was associated with prolonged, severe thrombocytopenia and leukopenia (lasting a median of 24 and 28 days, respectively). Treatment-related mortality was 19%. The benefit of melphalan dose intensification was confirmed by others who have used attenuated doses (50 to 70 mg/m<sup>2</sup>) and reported response rates of 50% to 85% (Barlogie et al. 1988).

#### 3.8.1.4.1.2 Cyclophosphamide as Induction Therapy

Since the original report by Korst et al. (Kyle 2000; Sporn and McIntyre 1986) of the utility of cyclophosphamide in myeloma patients, several single agent induction regimens have been studied. Despite documented equivalency for low-dose oral regimens of cyclophosphamide and melphalan, induction therapies of melphalan and prednisone tend to be preferred over those of cyclophosphamide and prednisone. The focus of study of cyclophosphamide for myeloma has been as an agent in multidrug combinations for induction, in relapse, and in stem cell mobilization. For newly diagnosed myeloma, however, oral daily dosing of cyclophosphamide (150 mg/d) or intravenously at dose levels of 600 mg/m<sup>2</sup> every 3 weeks with or without prednisone has resulted in a response rate of approximately 25% and median survival of 24 months (Sporn and McIntyre 1986).

#### 3.8.1.4.1.3 Corticosteroids as Induction Therapy

In previously untreated patients, approximately 43% have a 75% decrement in their *tumor mass index* with single agent high-dose dexamethasone therapy (Table 3.8) (Alexanian et al. 1992), which is only 15% lower than for vincristine, doxorubicin, and dexamethasone (VAD). Dexamethasone, in lieu of VAD for induction, in those patients destined for stem cell collection may be potentially advantageous. With single agent dexamethasone, insertion of a long-term central venous catheter can be postponed until conditioning for the stem cell transplantation, thereby reducing the likelihood of catheter-related complications (ie, thrombosis and infection). This strategy has been used successfully in this context, resulting in adequate collection of peripheral blood stem cells without any apparent adverse effect on complete remission rate or progression-free survival in a single-arm study.

#### 3.8.1.4.1.4 Interferon as Induction Therapy

Although the earliest studies of interferon suggested response rates of up to 60%, subsequent studies produced rates of 15% to 20% (Myeloma Trialists' Collaborative Group 2001). Ahre et al. randomized 55 patients to either melphalan and prednisone or interferon (3–6 MU daily); response rates in the melphalan and prednisone arm were significantly higher than in the interferon arm (44% versus 14%,  $P < 0.001$ ).

#### 3.8.1.4.1.5 Thalidomide as Induction Therapy

Thalidomide represents a new and distinct class of agents with significant activity against myeloma. When thalidomide is used as a single agent in previously untreated patients, response rates of about 35% may be achieved (Rajkumar et al. 2001; Weber et al. 2003). The combination of thalidomide and dexamethasone in previously untreated patients results in response rates of 68% to 72% (Rajkumar et al. 2002; Weber et al. 2003). Limited use of thalidomide pre-stem cell mobilization does not appear to impair stem cell collection or engraftment, although we tend to collect stem cells in patients after approximately 4 months of treatment. We typically suggest that patients have at least a 2-week washout period prior to stem cell mobilization efforts.



**Table 3.8. Corticosteroids**

Study	Agent	Schedule	Disease status	N	RR, %	Overall survival, mo
Adams and Skoog (Kyle 2000)	Corticosteroids	Various	All	NG	NG	NG
McIntyre et al. (Sporn and McIntyre 1986)	Pred	1.2 mg/kg per day → 70-day taper	Untr	32	44	21
Alexanian et al., 1992	Dex	40 mg/d d 1–4, 9–12, & 17–20; repeat every 42 d	Untr	112	43 <sup>a</sup>	NG
Salmon et al., 1998	Pred	200 mg qod × 8 wk → 100 mg qod × 4 → 50 mg qod	Ref, rel	10	80	NG
Alexanian et al. (Alexanian et al. 1992)	Pred	60 mg/m <sup>2</sup> d 1–5, 9–14, & 17–21; repeat every 42 d	Ref, rel	11	19 <sup>a</sup>	NG
Alexanian et al., 1992	Dex	40 mg d 1–4, 9–12, 17–20 q 5 wk	Ref Rel	30 19	27 <sup>a</sup> 21 <sup>a</sup>	NG
Forgeson et al., 1988	Methylpred	1 g/m <sup>2</sup> (max 1.5 g) d 1–5 q 21 d	Res Rel All	10 4	10 25	10
Gertz et al., 1995	Methylpred	2 g tiw × 8 wk, → 2 g/wk	Ref, rel	20	25	NG

Dex, dexamethasone; methylpred, methylprednisolone; NG, not given; po, by mouth; q, every; qd, daily; qod, every other day; ref, refractory; rel, relapsed; res, resistant; tiw, 3 times a week; untr, untreated.

<sup>a</sup> According to SWOG response criteria, response according to tumor mass index.

#### 3.8.1.4.2 Combination Chemotherapy (CCT) for Induction

A combination of the multiple active agents in an effort to achieve synergy was a logical corollary. For expediency, these regimens can be separated into 4 categories: alkylator-based without anthracycline, anthracycline-containing regimen, anthracycline-containing with intensified doses of corticosteroids, and induction regimens incorporating interferon. Thirty years of study indicate that multiagent combination chemotherapy as initial therapy results in higher response rates, but not longer overall survival, than standard melphalan and prednisone (Myeloma Trialists' Collaborative Group 1998). Although there has been a suggestion that patients with more advanced disease benefit from combination chemotherapy as compared to melphalan (Cooper et al. 1986; MacLennan et al. 1992), that hypothesis

has not been borne out (Myeloma Trialists' Collaborative Group 1998). In time, when we are better able to ascertain biologic differences between myeloma patients and properly classify them in a similar fashion to what is done in the field of lymphoma, a survival benefit with multiagent chemotherapy may be detected in particular subgroups.

##### 3.8.1.4.2.1 Alkylator-based Combination Chemotherapy Without Anthracycline for Induction

The 1970s and 1980s were a testing ground for various combinations of alkylators, corticosteroids, and doxorubicin. Melphalan/cyclophosphamide/prednisone, carmustine/cyclophosphamide/prednisone, melphalan/cyclophosphamide/carmustine/prednisone (MCBP), and vincristine/melphalan/cyclophosphamide/prednisone

(VMCP) resulted in response rates of 47%, 37% to 50%, 49% to 68%, and 62%, respectively (Alexanian et al. 1977). Median survivals with these regimens were 25 to 36 months. Case et al. (1977) introduced the 5-drug regimen of vincristine/carmustine/melphalan/cyclophosphamide/prednisone (VBMCP or the M-2 regimen), which included the same 4 drugs as MCBP plus vincristine; dose intensities, however, were different in these 2 regimens. Response rate for VBMCP was about 85% in previously untreated patients with a median survival of 38 months (Case et al. 1977). The success of the VBMCP regimen supported the value of vincristine. However, the MRC IV trial, which randomized 530 previously untreated patients with myeloma to melphalan and prednisone versus melphalan/vincristine/prednisone, revealed no difference in either response rate or overall survival between the 2 arms (MacLennan et al. 1992). VBMCP has not produced any response or survival advantage over melphalan and prednisone. Finally, the MOCCA regimen, which is essentially VBMCP with CCNU replacing BCNU, results in response rates similar to those for VBMCP (75%), but again a survival no different from melphalan and prednisone (Myeloma Trialists' Collaborative Group 1998).

Although subsequent randomized trials have substantiated the superior response rates of VBMCP over standard melphalan and prednisone (Table 3.9), they have not demonstrated superior survival. In fact, the meta-analysis performed by the Myeloma Trialists' Collaborative Group (1998), which included 6,633 patients and 27 randomized trials, revealed a superior response rate (60.2% versus 53.2%,  $P < 0.000001$ , 2-tailed) but no survival benefit for combination chemotherapy over standard melphalan and prednisone. A prior meta-analysis of 18 published trials (3,814 patients) also demonstrated no benefit for combination chemotherapy in terms of survival (Fig. 3.9). There might be a survival advantage in the subgroup of patients with more aggressive disease, but this has not been substantiated (Myeloma Trialists' Collaborative Group 1998).

#### 3.8.1.4.2.2 Combination Chemotherapy With Anthracycline for Induction

Alkylator- and doxorubicin-based combination chemotherapy arose from the report that the combination of doxorubicin and BCNU was beneficial in patients who had become resistant to melphalan (Alberts et al. 1976). Regimens like MAP (melphalan, doxorubicin,

and prednisone), CAP (cyclophosphamide, doxorubicin, and prednisone), VCAP (vincristine and CAP), and VBAP (vincristine, BCNU, doxorubicin, and prednisone) were tried; by SWOG response criteria, objective response rates were 41%, 46%, 64%, and 61% (Alexanian et al. 1977). Median survival ranged from 30 to 32 months; subsequent analysis demonstrated a superior median survival for the VBAP arm of 37 months (Crowley et al. 2001).

Enthusiasm for alternating VMCP and VBAP (or VCAP) was generated by the SWOG study of 237 patients randomized to melphalan and prednisone or these other 2 regimens (Table 3.9). Response rates were superior in the alternating combination chemotherapy arms compared to the melphalan arm. Survival was also superior in the combination chemotherapy arms (43 months versus 23 months for melphalan and prednisone,  $P = 0.004$ ). A subsequent analysis with longer follow-up showed less separation of the survival curves (median survival, 25 versus 36 months) (Crowley et al. 2001). The extent of survival benefit of this initial study has not been reproduced (Myeloma Trialists' Collaborative Group 1998).

The V MRC myelomatosis trial randomized patients to ABCM (VBAP/VMCP without the vincristine or prednisone) or melphalan as a single agent on the basis of their findings in the IV MRC trial, which demonstrated an absence of benefit of vincristine. Median survival in the ABCM group was superior to that of the melphalan only arm (32 versus 24 months,  $P = 0.0003$ ) (MacLennan et al. 1992).

#### 3.8.1.4.2.3 Combination Chemotherapy With Doxorubicin and Dose-Intensive Corticosteroids for Induction

The next level of combination chemotherapy includes those programs that include anthracycline and also contain high-dose corticosteroids. VAD-like regimens are commonly used as induction therapy pre-stem cell collection and transplantation. These regimens include VAP, VAD (Barlogie et al. 1984), VAMP (vincristine, doxorubicin, methylprednisolone), and C-VAMP (cyclophosphamide and VAMP) (Forgeson et al. 1988), all of which had been tried with salutary effect in relapsed disease. Subsequently, several of these regimens were applied in previously untreated patients and response rates were 50% to 84% (Alexanian et al. 1990). Median survival for patients treated initially with VAD is about

**Table 3.9. MP vs. combination chemotherapy as induction: selected randomized trials**

Study	Regimen	N	RR, % <sup>a</sup>	Overall survival, mo	P (RR)	P (OS)
SWOG 727/1972	MP	125	40 <sup>b</sup>	28	NS	NS
	MP-Pcb	116	47	31		
SECSG 343/1984	MP	187	29	36	NS	NS
	BCP	186	37	36		
CALGB 7161/1979	MP	126	56	NG	0.047	NS
	MCBP	124	68			
NCI-C-MY1/1979	MP	125	40 <sup>b</sup>	28	NS	NS
	MCBP	239	39	31		
ECOG 4472/1982	MP	92	40	19	NS	NS
	BCP	96	50	25		
GATLA3-M-73/1980 & 1988	MP	67	40	38	NS	NS
	CP-MeCCNU	83	40	30		
GATLA3-M-77/1984 & 1988	MP	145	33	42	NS	NS
	MPCV-MeCCNU	115	44	44		
Pavia MM-75/1986	MP	39	41	54	NS	0.039
	Pept-VP	36	58	26		
SWOG 7704/1983 & 1986	MP	77	32 <sup>b</sup>	23	0.001	0.004 <sup>c</sup>
	VMCP/VCAP	80	58	43		
	VMCP/VBAP	80	49	43		
MDA7704/1984	MP	30	53 <sup>b</sup>	38	NS	NS
	VMCP/VCAP	42	55	27		
	VMCP/VBAP	34	60	28		
CALGB 7761/1986	MP (IV)	146	47	34	NS	<sup>d</sup>
	MCBP	140	56	29		
	Seq-MCBP	148	47	22		
	MCBPA	157	44	26		
IMMSG M-77/1985	MP	47	19 <sup>b</sup>	30	NS	NS
	VMCP	53	19	45		
	BC-Pept	33	3	58		
Gentofte, Denmark/1985	MP	31	45	21	NS	NS
	VMP	32	73	30		
	VBMCP	33	58	21		
ECOG 2479/1997	MP	230	51	27	< 0.0001	NS
	VBMCP	235	72	29		
MRC MYEL-4/1985	MP	261	NG	26	NS	NS
	VMP	269		26		
Finnish MM80/1987	MP	66	54	41	<0.02	NS
	MOCCA	64	75	45		
Norwegian trial/1986 & 1988	MP	48	48	29	NS	NS
	VBMCP	44	54	33		

**Table 3.9** (continued)

Study	Regimen	N	RR, % <sup>a</sup>	Overall survival, mo	P (RR)	P (OS)
MGCS stage III/1989	MP	44	61	28	NS	NS
	VMCP/VBAP	42	52	24		
GMTG MM01/1988 & 1991	MP	170	33 <sup>b</sup>	60%	NS	< 0.02
	VMCP	150	33	4 y		
MGCS stage II/1990	MP	29	69	46	NS	NS
	VMCP	25	56	33		
MGCS stage III/1990	MP	55	58	26	NS	NS
	VMCP/VBAP	53	57	24		
IMMSG M-83/1991	MP	146	64	37	0.02	NS
	VMCP/VBAP	158	77	32		
PETHEMA 85/1993	MP	247	32	27	0.004	NS
	VMCP/VBAP	241	45	32		
Pavia 1986/1994	MP	87	24	All 24	NS	NS
	Pept-VP	83	24			
NMSG/1993	MP	74	64	31	NS	0.02
	NOP	77	60	14		
GMTG MM02/1995	MP (IV) <sup>e</sup>	99	43	~ 37	0.01	NS
	VBAMD <sup>e</sup>	105	64			
Meta-analysis (Myeloma Trialists' Collaborative Group 1998)	MP vs. CCT	6633	53	29	< 0.00001	NS
			60	29		

A, doxorubicin; B, BCNU or carmustine; C, cyclophosphamide; CCT, combination chemotherapy; D, dexamethasone; IV, intravenous; M, melphalan; MeCCNU, methyl-CCNU; MOCCA, the additional C is for CCNU (lomustine); NG, not given; NOP, mitoxantrone, vincristine, and prednisone; NS, not significant; P, prednisone; Pcb, procarbazine; Pept, peptichemo; V, vincristine.

<sup>a</sup> Except where stated, response is according to Myeloma Task Force criteria or modification.

<sup>b</sup> SWOG response criteria.

<sup>c</sup> Significantly superior survival in combination chemotherapy arms compared to MP in the 174 stage III patients but not in the 74 stage I or II patients.

<sup>d</sup> The sequential arm was significantly worse than either the MP ( $P=0.01$ ) or the MCBP ( $P=0.02$ ) and marginally worse than MCBPA ( $P=0.09$ ).

<sup>e</sup> Part of an interferon trial; stage III patients only.

Data from Myeloma Trialists' Collaborative Group (1998).

36 months. The complete response rate of C-VAMP is higher than for VAMP alone, but survival is no different. Several other variations have been reported in which alternative anthracyclines or corticosteroids were used.

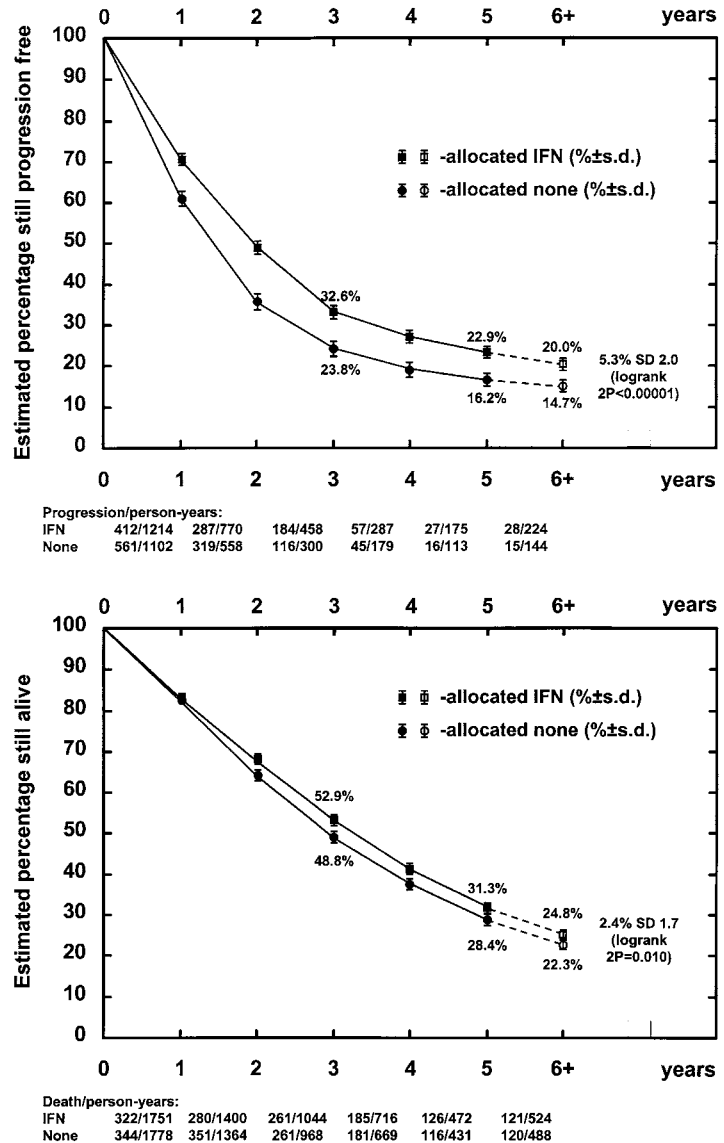
In a randomized trial of 151 patients comparing the NOP regimen (mitoxantrone, vincristine, and high-dose prednisone) to melphalan and prednisone, response rates were equivalent (~60%), but overall survival was inferior in the NOP arm (14 versus 31 months,

$P=0.02$ ). Response rates of 80% have also been achieved using the CAD (cyclophosphamide, doxorubicin, dexamethasone) regimen. The addition of etoposide to C-VAD appears to contribute only toxicity.

#### 3.8.1.4.2.4 Combination Chemotherapy With Interferon for Induction

Interferon has been combined with melphalan and prednisone; VMCP; VMCP/VBAP; prednisone, cyclophos-

**Fig. 3.10.** Interferon (IFN) chemotherapy as induction or maintenance therapy influences progression-free and overall survival curves from the meta-analysis by the Myeloma Trialists' Collaborative Group. Results from 24 randomized trials and 4,012 patients. Interferon curves include patients who received interferon as part of induction or of maintenance program. *A*, Progression-free survival after 23 months with interferon and 17 months without. *B*, Overall median survival after 40 months with interferon and 36 months without. (From the Myeloma Trialists' Collaborative Group [2001]. By permission of Blackwell Science.)



phamide, doxorubicin (Adriamycin), and carmustine (BCNU) (PCAB); VAD; VBMCP; VBAP; and cyclophosphamide as part of an induction regimen. Results have been mixed. Two meta-analyses have been performed in an attempt to reconcile these conflicting results (Ludwig and Fritz 2000; Myeloma Trialists' Collaborative Group 2001). The first, published in 2000 by Ludwig and Fritz, used published data and included 17 induction trials with 2,333 evaluable patients; the second, reported by the Myeloma Trialists' Collaborative Group in 2001, used primary data from 12 induction trials involving 2,469 pa-

tients. Overall, the results were similar. In the former analysis, the benefits of inclusion of interferon in an induction regimen were a 6.6% higher response rate ( $P < 0.002$ ) and a 4.8-month and 3.1-month prolongation of relapse-free ( $P < 0.01$ ) and overall survival ( $P < 0.01$ ) (Ludwig and Fritz 2000). In the second meta-analysis, patients receiving interferon had a slightly better response rate (57.5% versus 53.1%,  $P = 0.01$ ) and progression-free survival (30% versus 25% at 3 years,  $P < 0.0003$ ), with a superior median time to progression of about 6 months (Fig. 3.10). The survival advantage

of 2 months, however, was not significant ( $P=0.1$ ) (Myeloma Trialists' Collaborative Group 2001). A cost-effectiveness estimation for induction was also performed. The authors concluded that interferon administration and monitoring expenses amounted to \$US 41,319.28 to save a year of life of myeloma patients, assuming a dosage of 12.1 MU/week (Ludwig and Fritz 2000).

These meta-analyses suggest that incorporation of interferon into induction provides a modest prolongation of response and possibly of survival (Fig. 3.10). The question remains, however, whether these significant differences are clinically relevant.

### 3.8.2 Hematopoietic Stem Cell Transplantation

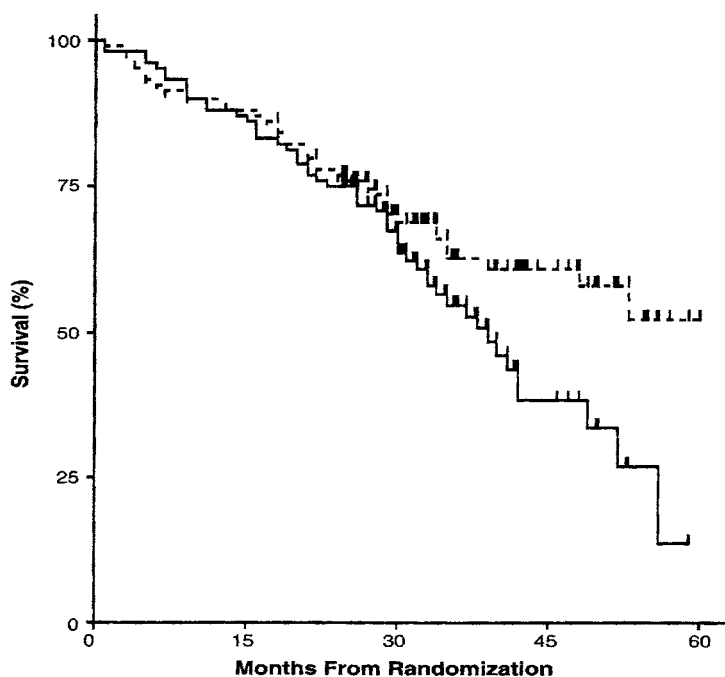
#### 3.8.2.1 Autologous Transplant

To overcome resistance of the myeloma cells to conventional-dose chemotherapy, McElwain and Powles (1983) pioneered the use of high-dose melphalan to treat multiple myeloma and plasma cell leukemia. The treatment was complicated by prolonged myelosuppression, and bone marrow (and later peripheral blood stem cell) support was subsequently incorporated. Barlogie et al. (1988) used a regimen combining high-dose melphalan

with total body irradiation supported by autologous bone marrow transplantation in multiple myeloma patients refractory to VAD.

Cure rarely if ever occurs, and almost all patients relapse after autologous stem cell transplantation. Although high-dose therapy followed by autologous stem cell transplantation is not curative, it improves response rate and survival (Barlogie et al. 1988; Dalton et al. 2001; Hahn et al. 2003; Harousseau and Attal 2002). Response rates with transplantation are 75% to 90%, and complete response rates are 20% to 40%. The results of single institution and phase 2 trials are difficult to analyze because selection of patients for transplantation is subject to selection bias regarding the stage of disease, performance status, age, and renal function.

The Intergroupe Français du Myelome (Attal et al. 1996) published the first randomized trial comparing high-dose chemotherapy followed by autologous bone marrow transplantation with conventional chemotherapy (Fig. 3.11). Two hundred patients with previously untreated multiple myeloma were randomized to receive high-dose chemotherapy followed by an autologous bone marrow transplantation or a combination of intravenous chemotherapy. The 5-year event-free survival (28% vs. 10%) and overall survival rates (52% vs. 12%) were higher



**Fig. 3.11.** Attal transplant curve. Dashed curve, high dose; solid curve, low dose. (From Attal et al. [1996]. By permission of the Massachusetts Medical Society.)



in the transplantation group. An updated analysis with a median follow-up of 7 years confirmed that high-dose chemotherapy improves event-free survival (median, 28 months vs. 18 months) as well as overall survival (median, 57 months vs. 44 months) (Dalton et al. 2001).

Autologous peripheral blood stem cell transplantation has replaced autologous bone marrow transplantation because engraftment is more rapid and there is less contamination with myeloma cells (Hahn et al. 2003). Hematopoietic stem cells should be collected before the patient is exposed to alkylating agents, because prolonged prior melphalan exposure predicts impaired collection of peripheral blood stem cells when either chemotherapy/growth factor or growth factor alone (Hahn et al. 2003) mobilization strategy is used. Even after 4 to 6 cycles of VMCP/VBAP, which is a regimen containing low doses of melphalan, in approximately 10% of patients, sufficient stem cells could not be collected for stem cell transplantation (Attal et al. 1996). In contrast, successful stem cell collection is achieved in 95% to 100% of multiple myeloma patients treated with VAD before mobilization with high-dose cyclophosphamide. The absolute number of CD34<sup>+</sup> cells/kg is the most reliable and practical method for determining the adequacy of a stem cell collection. The mortality rate from autologous stem cell transplantation is currently less than 5%. Age older than 65 years is not a contraindication for transplantation, although there are no randomized data proving or disproving its utility in this age group. Such patients are candidates for transplantation if they have good functional status and limited comorbidity (Hahn et al. 2003) (Fig. 3.8).

### 3.8.2.1.1 Transplantation for Primary Refractory Myeloma

In contrast to the experience with malignant lymphoma, stem cell transplantation appears to be effective for patients with primary resistant disease (Hahn et al. 2003). Patients with multiple myeloma in whom first-line therapy such as VAD fails can be sensitive to high-dose chemotherapy with stem cell reconstitution. In 1995 Alexanian et al. reported a decrease of 75% in tumor burden in 56% of patients and a marked improvement in survival compared with matched historical controls. Rajkumar et al. also looked at stem cell transplantation in primary refractory disease in 1999 and found no differences in overall and complete response rates between patients with primary refractory and relapsed disease.

The median survival of the entire cohort from diagnosis was 53 months.

### 3.8.2.1.2 Single Versus Double Transplantation

The role of double or tandem autologous stem cell transplantation is controversial. Barlogie and colleagues at the University of Arkansas advocate this approach of tandem (double) autologous stem cell transplantation to improve complete response rates and survival (Barlogie et al. 1999; Hahn et al. 2003). In tandem transplantation, patients receive a second planned transplant on recovery from the first procedure. In a study of 231 patients with newly diagnosed myeloma, the overall survival with this approach was 68 months (Barlogie et al. 1999). About 50% of patients in this cohort were age 50 years or younger and had less than stage III disease. These results have prompted several studies of stem cell transplantation in myeloma.

Preliminary data from 4 different randomized trials indicated a slight increase in response rates and possibly event-free survival with tandem transplantation (Dalton et al. 2001), but no clear improvement in overall survival (Table 3.10). As presented at the American Society of Hematology in 1997, with 2-year follow-up, there was no difference in event-free or overall survival between double and single autologous stem cell transplant in the IFM 94 trial that included 403 patients from France. In another evaluation of this study (Dalton et al. 2001), a subgroup of patients – those receiving stem cells derived from the peripheral blood rather than the bone marrow – had a modest overall survival benefit with tandem transplantation. There is no obvious explanation for the observed difference in survival between the groups. Most recently, the authors have reported in abstract form that this study is positive. Though the response rate was not significantly different between the 2 groups (complete response and very good partial response 42% in the single-transplant arm versus 50% of patients in the double-transplant group,  $P = 0.15$ ), both event-free survival and overall survival were improved in the double-transplant arm. Median survival in the 2 arms was not different, but the 7-year postdiagnosis probability of event-free survival was 20% (95% CI, 14–26) in the double-transplant arm versus 10% (95% CI, 5–15) in the single-transplant arm ( $P < 0.03$ ). Respective 7-year postdiagnosis overall survival rates were 42% (95% CI, 34–49) and 21% (95% CI, 13–29,  $P < 0.01$ ). In this trial 4 factors were associated with a

**Table 3.10.** Single versus double hematopoietic stem cell transplantation, randomized trials

Study	N	FU, mo	Event-free survival, % (years FU)			Overall survival, % (years FU)		
			Single	Double	P	Single	Double	P
IFM	403	60	19 (6)	28 (6)	0.03	26 (6)	46 (6)	0.02
Hovon	255	29	35 (3)	36 (3)	NS	47 (4)	43 (4)	NS
Bologna	178	30	21 mo (median)	29 mo (median)	NS	74 (4)	71 (4)	NS
MAG	193	27	41 events	43 events	NS	27 deaths	22 deaths	NS

FU, follow-up; NS, not significant.

Modified from Dalton et al. (2001). By permission of the American Society of Hematology.

longer survival: low  $\beta_2$ -microglobulin at diagnosis ( $P < 0.01$ ), young age ( $P < 0.05$ ), low LDH at diagnosis ( $P < 0.01$ ), and treatment arm ( $P < 0.05$ ). The final results of this and the other 3 trials listed in Table 3.10 will provide a definitive answer to the question of tandem transplantation. Because the role of tandem or double transplantation is not settled, it is reasonable to harvest enough stem cells for 2 transplants.

### 3.8.2.1.3 Timing of Transplantation

The timing of the transplantation, either up front as consolidation therapy or as salvage therapy at the time of relapse, is also a point of controversy. In one study (Ferland et al. 1998), 185 patients were treated with 1 to 2 cycles of intensified CHOP followed by PBSC collection and then randomized to 3 or 4 courses of VAMP followed by high-dose chemotherapy and autologous stem cell transplantation or to conventional chemotherapy (VMCP) until stable plateau, followed by autologous transplantation at disease progression. The median survival was essentially the same in both groups (65 months vs. 64 months). From the time of randomization, the median event-free survival in the early transplant group was 39 months compared with 13 months in the delayed transplant group. The main advantage of early transplantation was the avoidance of the inconvenience and cost of chemotherapy (Ferland et al. 1998). The North American Intergroup Study (S9321) is a larger randomized trial comparing early to late transplantation. It met its accrual goal of approximately 1,000 patients in October 2000. Results of this trial are not yet available.

### 3.8.2.1.4 Conditioning Therapy and Stem Cell Transplantation

In an effort to improve autologous stem cell transplantation, various preparative regimens have been used. There has been only one prospective randomized controlled trial comparing conditioning regimens in patients with myeloma (Moreau et al. 2002). Moreau et al. (2002) randomized 282 patients to either melphalan (140 mg/m<sup>2</sup>) plus total body irradiation or melphalan alone (200 mg/m<sup>2</sup>). There was no difference in response rate or event-free survival. Survival at 45 months favored the melphalan alone arm (65.8% vs. 45.5%,  $P = 0.05$ ). Toxicity with melphalan alone was significantly less. Most investigators have now discontinued the use of total body irradiation and give only melphalan (200 mg/m<sup>2</sup>) as the preparative regimen. Studies are being conducted with skeletal targeted radiation, ie, beta-emitting phosphonates that localize to bone.

### 3.8.2.1.5 The Role of Purging

In the setting of autologous stem cell transplant, there was concern regarding the role of potentially contaminated autograft in relapse. Purging marrow with cyclophosphamide derivatives or with monoclonal antibodies (Hahn et al. 2003) has proven feasible although associated with prolonged myelosuppression after transplantation. Schiller et al. demonstrated that CD34<sup>-</sup> selection of peripheral blood progenitor cells could provide effective hematopoietic support in a group of 55 patients with advanced multiple myeloma after myeloablative chemotherapy. Subsequently, 2 large phase 3 randomized trials have shown no clinical benefit to using CD34<sup>+</sup> selected autologous peripheral blood stem cells.

### 3.8.2.2 Allogeneic Transplant

Allogeneic transplantation eliminates the problem of tumor cell contamination of the stem cells that is inevitable with autologous stem cell transplantation. Further, there is evidence of a graft-versus-myeloma effect with allografting (Tricot et al. 1996). Allogeneic transplantation can lead to prolonged disease-free survival in a relatively small percentage of patients (Hahn et al. 2003). The high treatment-related mortality (approximately 30%) and significant toxicity from graft-versus-host disease have limited the role of this procedure in the treatment of myeloma (Bensinger et al. 1996; Gahrton et al. 1991) (Table 3.11). There have been 4 case-control or cohort-control studies comparing autologous to allogeneic stem cell transplant. The largest of these is that of Bjorkstrand et al. In their retrospective analysis of data compiled by the European Blood and Marrow Transplantation Group, there was inferior survival for myeloma patients treated with allogeneic bone marrow transplant compared to case-matched controls treated with autologous transplant (18 months versus 36 months) (Bjorkstrand et al. 1996). The 3 other smaller studies, which had relatively short follow-up, have shown mixed results with regard to progression-free survival and overall survival; transplant-related mortality, however, is consistently higher in the allogeneic groups (19%–25%).

In an effort to reduce transplant-related mortality, Lokhorst et al. (2000) (Table 3.11) compared autologous stem cell transplant to T-cell-depleted allogeneic stem cell transplant (Hahn et al. 2003). Myeloma patients were eligible if they had chemotherapy-sensitive disease. Genetic randomization was used. After 44 months median follow-up, overall survival had not yet been reached in either group. Transplant-related mortality in the allogeneic group was 18% compared with 4% in the autologous group.

In one series, only 5 of 80 patients were alive without evidence of disease at 4 to 7 years after an allogeneic bone marrow transplantation for their multiple myeloma (Bensinger et al. 1996). It must be emphasized that the majority of these patients had chemotherapy-resistant disease before transplantation. Outcomes have improved over time (Hahn et al. 2003). Gahrton et al. reported that of 690 allogeneic, matched, sibling donor transplants for multiple myeloma reported to the European Group for Blood and Marrow Transplantation registry, 334 were performed between 1983 and 1993 (all with bone marrow) and 356 between 1994 and 1998. The 3-year overall survival was 35% for transplant recipients during the earlier period and 55% for recipients of bone marrow transplants during the later period. The improvement in survival since 1994 was the result of a significant reduction in transplant-related mortality, from 46% to 30% at 2 years.

**Table 3.11.** Nonrandomized comparisons of autologous and allogeneic hematopoietic stem cell transplantation for multiple myeloma

Study	N	TRM, %	MS, mo	P
Bjorkstrand et al., 1996	189 Auto	13	34	0.001
	189 Allo	41	18	
Varterasian et al., 1997 (Hahn et al. 2003)	24 Auto	12	33.5	NS
	24 Allo	25	38.6	
Couban et al., 1997 (Hahn et al. 2003)	40 Auto	5	>48	<0.001
	22 Allo	27	7	
Reynolds et al., 2001 (Hahn et al. 2003)	35 Auto	6	>15	NS
	21 Allo	19	>27	
Lokhorst et al., 1999 (Hahn et al. 2003)	50 Auto <sup>a</sup>	4	>44	NS
	11 Allo <sup>a,b</sup>	18	>44	

MS, median survival; NS, not significant; TRM, treatment-related mortality.

<sup>a</sup> Chemotherapy-sensitive patients only.

<sup>b</sup> T-cell-depleted allogeneic stem cells.

**Table 3.12. Nonmyeloablative regimens for multiple myeloma**

Study	N	Diagnosis to NMA, mo (range)	Sibling/MUD allograft	Age, y (range)	NMA regimen <sup>a</sup>
Badros et al. (2002)	31	29 (8–164)	25/6	56 (38–69)	Melphalan 100
Giralt et al. (2002)	22	36 (3–135)	13/9	51 (45–64)	FM
Maloney et al. (2002)	54	2 <sup>b,c</sup>	NS	55 (39–71)	Auto → NMA (TBI 200 cGy; MMF)
Kroger et al. (2002)	17	11 <sup>b,e</sup>	9/8	51 (32–64)	Auto → NMA (FM-ATG-MTX)

ATG, antithymocyte globulin; CR, complete response; FM, fludarabine and melphalan; FU, follow-up; MM, multiple myeloma; MMF, mycophenolate; MTX, methotrexate; MUD, matched unrelated donor; NMA, nonmyeloablative transplant; NS, not stated; OS, overall survival; PFS, progression-free survival; PR, partial response; TBI, total body irradiation; TRM, treatment-related mortality.

<sup>a</sup> All studies used cyclosporine as part of the graft-versus-host prophylaxis program.

<sup>b</sup> Patients had NMA after induction (most commonly vincristine, doxorubicin, and dexamethasone) and a standard autologous peripheral blood stem cell transplantation.

Table continues on page 89.

Allogeneic transplantation produces higher rates of molecular complete responses. In a series of 229 myeloma patients, Martinelli et al. demonstrated that allogeneic transplantation resulted in a complete response from 38% compared with 22% after autologous transplantation ( $P < 0.01$ ) (Hahn et al. 2003). Among patients achieving a clinical complete response, 50% of the allogeneic transplant group had a molecular complete response compared with only 17% of those who had received an autologous transplant. The median relapse-free survival for those who had a molecular complete remission was 110 months compared with 35 months for those who did not. Moreover, in those with a molecular complete remission, the relapse rate was only 16% in the allogeneic group and 41% in the autologous group. This is strong evidence that molecular complete responses are associated with a longer relapse-free survival.

### 3.8.2.3 Donor Lymphocyte Infusions

A graft-versus-myeloma effect has been noted after the administration of donor peripheral blood mononuclear cells for relapse after allogeneic transplantation (Tricot et al. 1996). Eight of 13 patients with myeloma relapse after an allogeneic bone marrow transplant responded to donor lymphocyte infusions. Four of the patients had a complete response. In a larger group of patients with a prolonged follow-up period, the factors that were correlated with response to donor lymphocyte infusions were a T-cell dose of more than  $1 \times 10^8$  cells/kg, response to reinduction therapy, and chemotherapy-sensitive dis-

ease before the allogeneic transplantation (Lokhorst et al. 2000).

### 3.8.2.4 Nonmyeloablative Allogeneic Transplant

Despite a significant decrease in the relapse rate and graft-versus-myeloma effects, allografts have been associated with inferior survival in nearly all comparisons because of high peritransplantation mortality, late complications of chronic graft-versus-host disease (GVHD), and late infections. The mortality rate for allogeneic transplantation must be reduced before it can assume a major role in the treatment of multiple myeloma. Promising approaches include nonmyeloablative conditioning (“mini”) regimens for selected patients with myeloma, either at relapse or immediately after autologous stem cell transplantation.

Investigators from the University of Arkansas reported results of nonmyeloablative allogeneic stem cell transplantation in 31 poor-risk myeloma patients (Badros et al. 2002) (Table 3.12). Twenty-five were human leukocyte antigen-matched compatible siblings and 6 were unrelated and matched. The conditioning consisted of melphalan at 100 mg/m<sup>2</sup> for related and melphalan at 100 mg/m<sup>2</sup> plus total body irradiation (250 cGy) plus fludarabine for unrelated allografts. Donor lymphocyte infusions were initially given on days 21, 42, and 112 to patients with no clinical evidence of GVHD. However, because of a high incidence of GVHD, donor lymphocyte infusion was reserved to attain full donor chimerism or to eradicate residual disease. All

Median FU, mo	Patients in CR/PR, no.	TRM	MM deaths, no.	OS	PFS
6	12/10	9/31	3/31	31% at 24 mo	15 mo (median)
15	7/9	9/22	7/22	10 mo (median)	19% at 24 mo
18 <sup>d</sup>	NS	8/32	2/54	79% at 18 mo <sup>d</sup>	NS
17 <sup>d</sup>	11/3	2/17	1/17	74% at 24 mo	56% at 24 mo

<sup>c</sup> Time between autologous and NMA transplants.

<sup>d</sup> Time measured from autologous stem cell transplantation.

<sup>e</sup> Time to autologous transplant; time between transplants was 119 days.

but one patient had received 1 or more than 2 prior autologous transplants. Fifty-five percent of the patients had progressive disease at the time of the allograft. Acute GVHD developed in 18 patients. Ten patients progressed to chronic GVHD, limited in 6 and extensive in 4 patients. Two patients failed to engraft even after a second allogeneic peripheral blood stem cell infusion. At a median follow-up of 6 months, 12 patients achieved complete remission and another 7 near complete remission, and 3 achieved partial remission. There were 3 treatment-related deaths during the first 100 days and another 6 after 100 days, for an overall treatment-related mortality of 28%. Three patients died of progressive myeloma. Patients with progressive disease who received transplants or who had received more than 1 autograft had a statistically higher mortality rate. The authors also compared their nonmyeloablative transplant experience to their prior standard allogeneic experience and found that the nonmyeloablative group had a lower mortality during the first year ( $P = 0.09$ ), most notably the subset who had received only 1 prior autograft ( $P = 0.05$ ).

Maloney and colleagues (2002) reported results on 54 newly diagnosed myeloma patients who were treated with a planned tandem autologous/nonmyeloablative allogeneic stem cell transplantation (Table 3.12). After induction with 4 cycles of VAD chemotherapy, followed by autologous stem cell transplantation using melphalan 200 mg/m<sup>2</sup> as conditioning, patients underwent a nonmyeloablative allograft. The conditioning for the second transplant was with total body irradiation (200 cGy).

Matched sibling donor peripheral blood stem cells were infused immediately after the total body irradiation. Postgrafting immunosuppression included mycophenolate and cyclosporine. Fifty-two of the 54 patients received the planned nonmyeloablative transplant, with a median time between autologous and allogeneic transplant of 62 days. The granulocyte and platelet nadirs after the nonmyeloablative transplant were 760 cells/ $\mu$ L and 95,000 cells/ $\mu$ L, respectively. Acute GVHD was seen in 38% of patients and was grade II in all but 4 cases. Forty-six percent of patients developed chronic GVHD that required therapy. All patients achieved donor engraftment. Fifty-seven percent of patients not in complete response at the time of the second transplant achieved a complete response. With a median follow-up of surviving patients of 18 months, 8 patients (15%) have died of transplant-related complications, 2 of progressive myeloma, and 1 of lung cancer.

Kroger et al. (2002) have applied a similar strategy of a planned standard intensity autograft (melphalan 200 mg/m<sup>2</sup>) followed by a dose-reduced regimen (fludarabine 180 mg/m<sup>2</sup>, melphalan 100 mg/m<sup>2</sup>, and antithymocyte globulin 3 $\times$ 10 mg/kg) before allografting (Table 3.12). GVHD prophylaxis included cyclosporine and mini-methotrexate. Nine patients received allografts from related donors and 8 from unrelated donors. Acute GVHD stage II-IV occurred in 6 patients (38%). Chronic GVHD developed in 40% of the patients, but only 1 patient experienced extensive chronic GVHD requiring further immunosuppressive therapy. The 100-day mortality rate was 11%, and with a median follow-up of 17



months after autologous and 13 months after allogeneic transplantation, 13 patients (76%) are alive. The rate of complete remission with negative immunofixation increased from 18% after autografting to 73% after allografting, and 12 remain free of relapse or progression.

Until further refinements are made and additional confirmatory studies are completed, the role of nonmyeloablative allogeneic stem cell transplantation as initial therapy in myeloma must be considered investigational. See Table 3.12 for additional preliminary data.

### 3.8.2.4.1 Maintenance Therapy

Maintenance therapy strategies can be divided into 2 broad categories: 1) continued induction therapy ad infinitum, and 2) addition of a novel therapy after induction therapy. The former strategy was prevalent until recognition of the risk of alkylator-induced myelodysplastic syndrome and leukemia. The latter strategy has predominantly applied immune modulators, including prednisone, interferon, and cellular therapies.

#### 3.8.2.4.1.1 Maintenance Chemotherapy

Through the 1970s and 1980s, several randomized studies established that alkylator-based maintenance therapy does not produce a survival benefit (Belch et al. 1988; Cohen et al. 1986; MacLennan et al. 1992; Riccardi et al. 2000; Southwest Oncology Group Study 1975). In general, unmaintained patients had similar to slightly shorter remission duration than those receiving maintenance (Alexanian et al. 1978; Belch et al. 1988; Cohen et al. 1986; Riccardi et al. 2000) but had higher rates of second remission (Alexanian et al. 1978; Belch et al. 1988). In some studies there has been a trend toward longer survival in patients not receiving maintenance chemotherapy (MacLennan et al. 1992; Southwest Oncology Group Study 1975). Induction therapy is commonly discontinued after plateau is reached (no change in M protein more than 25% for 4 to 6 months). In the context of standard therapy, the ability to achieve a plateau is as important, if not more important, as depth of response to therapy (Bladé et al. 1994; Corso et al. 1999; Finnish Leukaemia Group 1999; Riccardi et al. 2000). No benefit has been documented for treatment beyond 12 months, although it has been suggested – but not validated – that prolonged primary chemotherapy may be beneficial in patients achieving less than a partial response, ie, a minimal response or stable disease (Oivanen et al. 1999).

Patients who relapse off chemotherapy have response rates of 25% to 80% with resumption of the original regimen (Alexanian et al. 1978; Belch et al. 1988; Riccardi et al. 2000). Second response rates are lower in patients who progress or relapse during maintenance than in those who relapse during no maintenance (Alexanian et al. 1978; Cohen et al. 1986). In a study of 115 newly diagnosed patients treated with the M-2 regimen (VBMCP) for about 1 year, an initial response rate of 82% was achieved, with a median duration of response of 22 months. After a first relapse, 26 of 38 patients (68%) responded again and had a median duration of response of 11 months. After a second relapse, 7 of 16 patients (44%) responded, with a duration of response of 3.5 months (Paccagnella et al. 1991).

#### 3.8.2.4.1.2 Corticosteroids as Maintenance Therapy?

There are 4 studies that refer to the topic of corticosteroids as maintenance therapy. None justify a recommendation of prednisone as a standard maintenance regimen for all patients.

The most recent study (SWOG 9210) compared prednisone 10 mg every other day to prednisone 50 mg every other day in patients who had responded (SWOG PR or better) to 6 to 12 months of a VAD-based program, that is, a corticosteroid-intensive program. From the time of the randomization to the 2 different alternate-day prednisone schedules, the median progression-free survival for the higher-dose prednisone arm was 14 months compared with 5 months ( $P=0.003$ ). Survival was also marginally better at 37 and 26 months ( $P=0.05$ ) (Berenson et al. 2002). Although the more dose-intensive corticosteroid maintenance strategy does provide a longer progression-free survival in corticosteroid-responsive patients, these data cannot be generalized and must be placed into context. By comparison, after alkylator-based therapy the median unmaintained progression-free survival is 12 months in responding patients (Cohen et al. 1986).

An earlier randomized study, which compared dexamethasone maintenance to interferon maintenance after induction with melphalan and dexamethasone, demonstrated equivalence to inferiority of dexamethasone compared with interferon. Patients received maintenance treatment with interferon- $\alpha$  (3 MU 3 times a week) or dexamethasone (20 mg/m<sup>2</sup> orally each morning for 4 days, repeated monthly) until relapse. Remis-

sion duration was identical (10 months); however, significantly more patients responded on reinstatement of the melphalan and dexamethasone at disease relapse in the interferon group than in the dexamethasone group (82% versus 44%,  $P=0.001$ ) (Alexanian et al. 2000).

The CALGB 7461 study as reported by Cornwell et al. (1988) addressed this issue less directly. Patients were treated initially with alkylator therapy and randomized to observation or vincristine and prednisone as maintenance. Survival and response rates were significantly longer and higher in the vincristine-prednisone maintenance group who had received up-front melphalan (median, 35.3 months versus 27.0 months;  $P=0.003$ ) but not in patients who had received up-front BCNU or CCNU (Sporn and McIntyre 1986).

Finally, SWOG 8624, which evaluated the influence of corticosteroid dose intensity on response and survival, indirectly provides data on corticosteroid maintenance. Higher objective response rate and median survival were observed in patients who received prolonged administration of glucocorticoids (prednisone 50 mg every other day) between chemotherapy courses. Patients given VMCP/VBAP with and without alternate day prednisone had median overall survivals of 40 months versus 31 months, respectively ( $P=0.02$ ). The survival advantage may have been confounded by the complexity of the study; different treatment plans were assigned after 12 months of induction therapy, determined by tumor response. Moreover, one could argue that the corticosteroid was more a part of the induction than of the maintenance program.

### 3.8.2.4.1.3 Interferon as Maintenance Therapy

#### 3.8.2.4.1.3.1 After Conventional Chemotherapy

The initial findings by Mandelli et al. in 1990 of a superior disease-free and overall survival in chemotherapy-responsive patients randomized to maintenance interferon- $\alpha$  have been challenged by multiple subsequent studies. Ludwig and Fritz (2000) analyzed 1,615 patients from 13 maintenance trials, and the Myeloma Trialists' Collaborative Group (2001) used the individual data of 1,543 patients enrolled in 12 randomized maintenance trials for meta-analysis. Results were similar in that the first group found a 4.4-month and 7.0-month prolongation of relapse-free ( $P<0.01$ ) and overall survival ( $P<0.01$ ), respectively (Ludwig and Fritz 2000). The latter group reported that interferon- $\alpha$  prolonged the median

time to progression by about 6 months ( $P<0.00001$ ) and overall survival by approximately 7 months ( $P=0.04$ ) (Myeloma Trialists' Collaborative Group 2001) (Fig. 3.8). Survival from progression to death was significantly worse in the interferon group than in the control group (odds ratio 1.21,  $P=0.007$ ). No factors analyzed predicted for the interferon benefit (ie, pretreatment hemoglobin, calcium,  $\beta_2$ M, creatinine, sex, performance status, or immunoglobulin isotype). The level of response (complete response, partial response, stable disease) or interferon dose intensity (<12 MU/week versus  $\geq 12$  MU/week) also did not predict for interferon effect (Myeloma Trialists' Collaborative Group 2001). The cost in 2000 of the 1-year survival benefit in patients treated with interferon as maintenance was \$US 18,968.16, assuming a dose of 11.6 MU/week (Ludwig and Fritz 2000).

#### 3.8.2.4.1.3.2 In Combination With Corticosteroids

Corticosteroids have been added to maintenance interferon in an attempt to intensify the program. Small numbers of patients have been treated with standard maintenance interferon and either dexamethasone or prednisone (Salmon et al. 1998). In one small randomized study, the progression-free survival was longer in the corticosteroid plus interferon arm than in the interferon only arm, although median survival was not different (Salmon et al. 1998). The combination can also induce further partial remissions in more than half of responding patients treated.

#### 3.8.2.4.1.3.3 After High-Dose Chemotherapy With Stem Cell Support

Fewer data are available about the utility of interferon after autologous stem cell transplantation. There is one small randomized trial of 85 patients and a larger retrospective analysis of registry data by the European Group for Blood and Marrow Transplantation (EBMT). The use of interferon in this setting cannot be recommended outside of clinical trials.

After high-dose chemotherapy with stem cell support, Cunningham et al. (1998) randomly assigned 85 patients to interferon at 3 MU/m<sup>2</sup> 3 times weekly or to observation. The median progression-free survival in the 43 patients randomized to interferon- $\alpha$  was 46 months compared with 27 months in the control patients ( $P<0.025$ ). Although there was a significant survival advantage at 54 months, at which time 12% of pa-

tients in the interferon group and 33% of patients in the no interferon group had died ( $P=0.006$ ), this survival advantage was no longer evident at a median follow-up of 77 months (Cunningham et al. 1998).

The EBMT registry study data included 473 patients who had received maintenance and 419 who had not. Unfortunately, the 2 groups were poorly matched. The patients who did not receive interferon had significantly more prior therapy, a higher stage at diagnosis, and a longer time to transplantation. They were also significantly older and a higher percentage had received total body irradiation-containing conditioning regimens (Bjorkstrand et al. 2001). Although these factors were “statistically corrected for” in the survival analysis, this imbalance makes interpretation of this retrospective collection of registry patients problematic. Prognostic factors like  $\beta_2M$ , C-reactive protein, cytogenetics, and PCLI were not included in the analysis. Overall survival was significantly better in the patients who received interferon (78 versus 47 months,  $P=0.007$ ). Curiously, there was a more prominent survival benefit in those patients who achieved partial response (97 versus 46 months for interferon versus no interferon,  $P=0.03$ ) rather than complete response (64 versus 51 months,  $P=0.1$ ). Paradoxically, the partial response group had a better overall survival than the complete response group.

#### 3.8.2.4.1.4 Immunotherapy as Maintenance Therapy

##### 3.8.2.4.1.4.1 Dendritic Cell-based Vaccination

In an effort to prolong duration of response and hopefully survival, idiotype-treated dendritic cell vaccines are being explored as a therapeutic modality for myeloma patients. B-cell malignancies, including multiple myeloma, are unique in their expression of immunoglobulin. The immunoglobulin on malignant cells can be distinguished from that on normal B cells or plasma cells by virtue of specific idiotypic determinants. Dendritic cells are the only known natural cells that can present antigen to naive T cells. Antigen pulsed dendritic cells can successfully induce both humoral and cytotoxic cellular immune responses.

Idiotypic vaccinations alone have met with limited success in human trials. However, dendritic cell-based vaccination appears to be a more potent way to induce antitumor immunity than vaccines with peptide alone. Trials are ongoing looking at dendritic cell-based vacci-

nations for multiple solid tumors as well as for myeloma, non-Hodgkin lymphoma, chronic myelogenous leukemia, and other hematologic malignancies. Preliminary evidence suggests that idiotype pulsed dendritic cells can stimulate anti-idiotype responses (Titze et al. 2000). Clinical responses have also been observed by us and other investigators in the setting of relapsed disease and after hematopoietic stem cell transplantation (Titze et al. 2000).

#### 3.8.2.4.2 Management of Relapsed or Refractory Disease

Relapsed and refractory myeloma likely have distinct biologies but are commonly grouped together in discussions of chemotherapy regimens and trials. Differentiation between relapses occurring on therapy and off therapy should be made, with the former having a poorer prognosis. Similarly, primary refractory – the condition in which the disease has not responded to initial therapy – and secondary refractory (or resistant) disease – should be differentiated. Finally, with the growing list of active agents, clarification should be made as to which class of agents or modality the myeloma is refractory.

Before the advent of high-dose chemotherapy with stem cell support and of thalidomide, treatment guidelines were more straightforward. If the relapse had occurred during an unmaintained remission, resumption of the patient’s original therapy was a good rule. Fifty percent to 60% of patients respond again to repeat treatment if relapse occurs after unmaintained remission (Alexanian et al. 1978; Belch et al. 1988; Paccagnella et al. 1991). Median survival is about 10 months (Alexanian et al. 1978). The myeloma cell doubling time and duration of response tend to decrease with each subsequent course of therapy (Paccagnella et al. 1991). In the cases of primary refractory disease or acquired resistance on therapy, the mainstays of treatment had been clinical trials, anthracycline-based, corticosteroid-based, and alkylator-based regimens, which might vary in schedule and dose intensity.

##### 3.8.2.4.2.1 Single Agent Glucocorticoids for Relapsed or Refractory Disease

Salmon et al. described clinical improvement in 7 of 9 relapsed or refractory patients treated with high-dose (200 mg) prednisone every other day. Subsequently, these observations (Table 3.8) were confirmed and ex-

tended using prednisone, methylprednisolone, and dexamethasone in pulsed or alternate-day schedules (Alexanian et al. 1990; Gertz et al. 1995). Doses are typically high, with the exception of one small study in which continuous low-dose dexamethasone (4 mg/day) was administered to a small cohort of patients, with a resultant 40% response rate. Overall, approximately 25% of relapsed or refractory patients respond; median survival of responding patients is 16 to 22 months (Alexanian et al. 1990; Gertz et al. 1995). In reviewing their experience with single agent dexamethasone and VAD, Alexanian et al. noted that in patients with refractory disease, response rates with single agent dexamethasone are comparable to those with VAD (27% versus 32%). In contrast, in relapsed disease, response rates achieved with single agent dexamethasone are inferior to those with VAD (Alexanian et al. 1990). These data are not randomized but rather serial observations. On occasion, patients who do not respond to high-dose dexamethasone can be salvaged with intermittent high-dose methylprednisolone (Gertz et al. 1995).

#### 3.8.2.4.2.2 Thalidomide for Relapsed or Refractory Disease

The first published report of the utility of thalidomide in patients with relapsed myeloma was by Singhal et al. Eighty-four patients with relapsed myeloma, 76 of whom had relapsed after high-dose chemotherapy with stem cell support, were treated with escalating doses of thalidomide. Patients were started on 200 mg each evening; the dose was escalated every 2 weeks if tolerated to a final maximal dose of 800 mg daily. Twenty-five percent of patients had at least a 50% reduction in their serum myeloma protein, and an additional 6 patients had a 25% reduction in their serum myeloma protein (minimal response). Preliminary evidence of response was apparent within 2 months in more than three-quarters of the patients who did respond. An update by Barlogie et al. of the original report, including 169 patients with advanced myeloma, verified a 30% response rate (50% reduction in the myeloma protein). Two-year event-free and overall survival rates were 20% and 48%, respectively. These findings have been substantiated by other investigators (Rajkumar et al. 2000).

The role of dose intensity in thalidomide effectiveness is unclear. In the original reports, the highest dose tolerated was administered. In high-risk patients there was a suggestion that response rates were higher and

survival longer in those patients receiving high doses of thalidomide (greater than or equal to 600 mg/day). However, in some patients, responses may be seen with doses as low as 50 to 100 mg/day.

There is synergy with thalidomide and dexamethasone. Response rates of 41% to 55% (Dimopoulos et al. 2001; Palumbo et al. 2001) have been observed in patients with resistant myeloma. Patients who are resistant to dexamethasone-based or thalidomide-based regimens can respond to the combination of these 2 agents (Dimopoulos et al. 2001). Coleman et al. described a 100% response rate for relapsed or refractory disease treated with clarithromycin, low-dose thalidomide, and dexamethasone. These results have yet to be substantiated by other investigators, and clarithromycin alone is not an effective treatment.

Toxicities associated with thalidomide include fetal malformations, constipation, weakness or fatigue, somnolence, skin problems, and sensory neuropathy in more than one-third of patients. There is also an increased risk of thrombosis in patients treated with thalidomide, which appears to be exacerbated by the use of concurrent combination chemotherapy, with rates as high as 28%. Other life-threatening complications have included Stevens-Johnson syndrome and hepatitis.

#### 3.8.2.4.2.3 Chemotherapy for Relapsed or Refractory Disease

The subject of chemotherapy for relapsed or refractory disease will be divided into 4 sections: alkylator-based regimens, anthracycline-based regimens with or without dose-intensified corticosteroids, and other less commonly used regimens.

##### 3.8.2.4.2.3.1 Alkylator-based Regimens for Relapsed or Refractory Disease

There is cross-resistance among the alkylators, but it is not absolute and may be circumvented by increasing dose intensity. Without extreme dose intensification, 5% to 20% of patients with melphalan-resistant disease respond to cyclophosphamide and BCNU as single agents or in combination with prednisone. About one-third of patients will respond if prednisone is administered with the cyclophosphamide (de Weerd et al. 2001).

Higher doses of cyclophosphamide (eg, 600 mg/m<sup>2</sup> intravenously for 4 consecutive days) result in response rates of 29% to 43% (Lenhard et al. 1994). Both response

duration and overall survival tend to be short, approximately 3 and 9 months, respectively. Consolidating the chemotherapy into a 1-day schedule rather than a 4-day schedule did not improve response rate, but it did increase the toxicity.

Dose intensification of melphalan can also be quite effective and is the basis for high-dose therapy with stem cell support (McElwain and Powles 1983). Selby et al. (1987) reported that 66% of patients with resistant disease treated with 140 mg/m<sup>2</sup> without stem cell support responded, but median response duration was 6 months, with all patients relapsing within a year. Median times to leukocyte and platelet recovery were 42 and 37 days, respectively, and the regimen-related toxicity was 13%. Doses of 30 to 70 mg/m<sup>2</sup> have also been explored.

VBMCP (the M-2 regimen) or MOCCA provides responses in 20% to 30% of refractory patients, with a median survival of about 11 months.

#### 3.8.2.4.2.3.2 Anthracycline-based Regimens Without Corticosteroid Dose Intensification for Relapsed or Refractory Disease

Various permutations of doxorubicin-containing chemotherapy regimens – doxorubicin and cyclophosphamide (Alberts et al. 1976); doxorubicin, BCNU, cyclophosphamide, and prednisone; CAP; VCAP; VBAP; and BAP – have been tried in patients with relapsed and refractory disease, resulting in response rates of 7% to 28% (Bonnet et al. 1982; Kyle et al. 1982). Response duration and survival tend to be short – less than 6 and 12 months, respectively. Responding patients tend to live 7 to 10 to even 22 months longer than nonresponders. Patients who have relapsed disease, rather than resistant or refractory disease, have higher response rates (i.e., close to 30%).

#### 3.8.2.4.2.3.3 Anthracycline-based Regimens With Corticosteroid Dose Intensification for Relapsed or Refractory Disease

Another approach to treating relapsed or refractory myeloma is supplementation of the anthracycline and vincristine with high-dose corticosteroids. Alexanian et al. (Barlogie et al. 1984) described VAP (bolus vincristine 1.5 mg day 1, doxorubicin 35 mg/m<sup>2</sup> day 1, and prednisone 45 mg/m<sup>2</sup> for 5 days repeated every 8 days for 3 corticosteroid pulses); response rates were 47%. Barlo-

gie et al. (1984) published their experience with VAD, and numerous variants have followed. The overall response rate with VAD in 29 patients who had refractory or resistant disease was 59%, according to SWOG criteria. In the 20 patients who had not received prior doxorubicin, the response rate was 70%. VAD differed from VAP in that the former included continuous infusion vincristine and doxorubicin and a 6-fold corticosteroid dose intensification. The activity of VAD has been substantiated by others. Infection is the most important complication, with 38% of patients having fever and 28%, a documented infectious agent. Early catheter removal may occur in approximately 16% of patients as a result of thrombosis or infection.

Variants of VAD include regimens that alter the type or dose of corticosteroid, schedule of administration, and type of anthracycline and additional drugs. The effectiveness of VAMP (methylprednisolone in place of dexamethasone) appears comparable to VAD, with a response rate and overall survival of 36% and 20 months in patients with resistant disease (Forgeson et al. 1988).

Alternative anthracyclines have been tried, including mitoxantrone (NOP or mitoxantrone, vincristine, and dexamethasone), epirubicin, and liposomal doxorubicin. Several investigators have added additional drugs to the VAD-base without measurable benefit. Concurrent interferon (Gertz et al. 1995) adds nothing to response rate or overall survival. In single-arm studies, there does not appear to be any advantage to the addition of cyclophosphamide to VAD, VAMP, or vincristine, epirubicin, and dexamethasone (VED) (Alexanian et al. 1992; Forgeson et al. 1988).

#### 3.8.2.4.2.3.4 Other Regimens for Relapsed or Refractory Disease

After studying high-dose cytosine arabinoside, cisplatin, and etoposide as single agents, Barlogie et al. (1989) did preliminary studies of DAP (dexamethasone, cytosine arabinoside, and cisplatin) and later EDAP (etoposide and DAP). In patients with refractory disease, response rates with these treatments were 7%, 14%, 17%, 0%, and 40%, respectively. Median survival in patients treated with EDAP was 4.5 months. This regimen is extremely myelosuppressive, with more than half of treated patients requiring platelet transfusions and 80% requiring hospitalization for neutropenic fever. In the first month, treatment-related mortality was 15%. EDAP is part of Barlogie's "Total Therapy II."



As part of Total Therapy II, before 2 cycles of EDAP, 55% and 9% of patients had achieved objective response and complete response, respectively; after EDAP, 65% and 15% had objective response and complete response (Barlogie et al. 1999).

Dimopoulos et al. explored a combination of high-dose cyclophosphamide (3 g/m<sup>2</sup>) and etoposide (900 mg/m<sup>2</sup>) followed by granulocyte-macrophage colony-stimulating factor. Of the 52 patients with advanced and refractory multiple myeloma treated, 42% responded. Median time to granulocyte recovery was 19 days, and the median remission duration was 8 months.

Combinations of cisplatin with BCNU, cyclophosphamide, and prednisone have produced response in heavily pretreated patients; however, the addition of cisplatin and bleomycin to VBAP did not appear to produce better outcomes than standard VBAP (Barlogie et al. 1989).

#### 3.8.2.4.3 Clinical Trials and New Agents

Until myeloma is a curable disease in all patients, clinical trials will play a critical role in the treatment of these patients. They will assist in defining a better classification system for the disease, clarify which treatments offer the most value, and bring new effective agents into standard clinical practice.

The 2 most promising new agents for the treatment of multiple myeloma are PS-341 and CC-5013 (Richardson et al. 2002), both of which are still in clinical trials. PS-341 is a small molecule that selectively inhibits cellular proteasomes, offering a novel pathway for targeted anticancer therapy. The proteasome has a key role in protein degradation, cell-cycle regulation, and gene expression. Tumor cells, including multiple myeloma, are heavily dependent on proteasome-regulated proteins for their growth and interaction with stromal cells. PS-341 generally has been well tolerated in phase 1 trials, with apparent clinical activity in patients with multiple myeloma. PS-341 represents a novel anticancer agent with an acceptable safety profile and evidence of anti-tumor activity in multiple myeloma. Partial or complete responses are observed in 27% of patients with relapsed or refractory disease or both (Richardson et al. 2003).

CC-5013, a small molecule derivative of thalidomide and a member of the immunomodulatory drug (IMiD) class, is more potent than thalidomide in mediating direct cytokine-related and immunomodulatory effects

against human multiple myeloma cell lines and patient-derived cells in vitro. During the 2 recently completed phase 1 studies, activity has been documented in patients with refractory or relapsed multiple myeloma. Approximately 25% of relapsed or refractory patients have achieved a partial response. Another 25% to 35% of patients have had a minimal response (25%–49% reduction in serum M component). No significant somnolence, constipation, or neuropathy has been seen (Richardson et al. 2002).

The human anti-CD20 antibody has demonstrated some effect in patients with myeloma. About 20% of patients with myeloma have CD20 expression on their plasma cells. Preliminary data suggest that use of this agent may be beneficial in this subset of patients.

### 3.8.3 Radiation

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As early as the mid-1920s there was recognition that external beam radiation therapy could promote immediate relief of pain, healing of pathologic fractures, and resolution of extramedullary plasmacytomas (Geschickter and Copeland 1928). Until the 1950s, radiation therapy was the only effective treatment available for the management of plasma cell tumors. With the advent of systemic chemotherapy, indications for irradiation were primarily palliation of bone pain and solitary plasmacytomas. Concern for maintaining bone marrow reserve also constrains the use of radiation in patients with multiple myeloma. The majority of patients receiving concentrated local doses of 3,500 cGy or more showed persistent localized marrow aplasia. One must administer enough radiation to provide palliation, without jeopardizing opportunities for further systemic therapy.

#### 3.8.4 Sequential Half-body (Hemibody) Irradiation

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The first report of using whole body irradiation to treat myeloma was by Medinger and Craver in 1942. Partial or complete relief of pain was noted in the majority of patients. Once effective systemic chemotherapy came into wide use, this approach became less popular until 1971 when Bergsagel postulated that sequential hemibody radiation could be a means to debulk tumor. He suggested that if a dose of approximately 725 cGy were given to the upper half of the body and 1,000 cGy to the lower half, a

theoretical 3-log kill could be achieved and survival prolonged. After a series of retrospective studies and a randomized study (Salmon et al. 1990) evaluating its role in the earlier phases of myeloma, irradiation has once again largely fallen out of favor. In patients who have end-stage disease, with poor pain control, this treatment may still be important.

The majority of series involving hemibody or sequential hemibody radiation are retrospective and include patients who were either resistant to or relapsing from alkylator-based therapy. Significant relief of bone pain occurred in 80% to 90% of patients, and median duration of survival was 5 to 11 months. Objective biochemical response occurred in 25% to 50%. Pain relief typically occurred 1 to 2 days after institution of therapy, with maximal response in 1 to 2 weeks. The most common side effects were moderate myelosuppression, pneumonitis, nausea, vomiting, diarrhea, and stomatitis. If an oral lead shield was not used, mucositis also occurred. Nadirs occurred within 3 weeks, and white cell count and platelet count recovery occurred by about 6 weeks. Decrements in pulmonary function of 20% occurred in about half of treated patients. The most serious complication was radiation-induced pneumonitis, which was seen in 14% of patients. The option of sequential half-body radiation therapy must be balanced against unpredictable and varying degrees of pancytopenia and alternative treatment options.

Bergsagel's postulate and preliminary data from several small studies led 2 cooperative group studies (SWOG 8229 and CALGB 8003) to incorporate systemic radiation therapy as consolidation therapy. Neither study demonstrated meaningful advantage to patients receiving adjuvant hemibody radiation (Salmon et al. 1990), and hemibody radiation is used only for pain palliation in end-stage chemotherapy-refractory myeloma patients.

### 3.9 Staging and Prognosis

Survival of multiple myeloma patients varies from months to more than a decade. There are no precise methods of identifying the subset of newly diagnosed patients who are best served by standard intensity therapies, by maintenance therapies, by novel therapies, or by more intensive regimens such as hematopoietic stem cell transplantation. Prognostic factors are needed

for patient counseling, therapeutic decision making, and clinical trial stratification.

Staging is one form of prognostic modeling. The Durie-Salmon system (Table 3.13), which is the most widely accepted multiple myeloma staging system, separates patients predominantly by tumor burden and renal function (Durie and Salmon 1975). As the biology of myeloma is better understood, novel markers reflecting myeloma cell kinetics, signaling, genetic aberrations, and apoptosis have eclipsed the prognostic significance of tumor burden as a predictor of survival.

Although the Durie-Salmon system has some prognostic value (Durie and Salmon 1975), other biologic variables appear to be more valuable (Bataille et al. 1992; Crowley et al. 2001; Greipp et al. 1993; Konigsberg et al. 2000). At the time of its inception, the Durie-Salmon staging system was an elegant system that incorporated information about immunoglobulin production and half-life, hemoglobin, calcium, creatinine, and extent of bone disease to derive mathematically the total myeloma cell burden. Quantification of bone lesions used in this staging system, however, is not always reliable as a prognostic factor in that patients classified as stage III only because of bone lesion criteria do not have a poorer prognosis.

Other variables, including patient age, performance status, serum albumin, immunoglobulin isotype, and bone marrow plasma cell infiltration, have long been recognized to predict survival, and subsequent models have incorporated these factors (Bartl et al. 1987; Finnish Leukaemia Group 1999; Medical Research Council's Working Party on Leukaemia in Adults 1980) (Table 3.14). Myeloma biology is better addressed by increased concentrations of serum  $\beta_2$ M, C-reactive protein, circulating plasma cells by peripheral blood labeling index, other serum markers, bone marrow PCLI, and chromosomal abnormalities (Bataille et al. 1992; Crowley et al. 2001; Greipp et al. 1993; Konigsberg et al. 2000). Each of these systems has value, but the goal is to reach a consensus and to standardize discussions and comparisons among clinical trials and outcomes. An international consensus panel is addressing this. When designing a new staging system, the dilemma exists regarding the use of readily available, inexpensive markers – which frequently describe the host more than the intrinsic properties of the myeloma – or more esoteric, expensive markers – which reflect the individual patient's myeloma biology. Table 3.14 summarizes several investigators' efforts to introduce more meaningful staging systems.

Criterion	Measured myeloma cell mass, cells $\times 10^{12}/m^2$
<b>Stage I</b> All of the following Hemoglobin >10 g/dL Serum calcium <12 mg/dL On radiograph, normal bone structure (scale 0) <sup>a</sup> or solitary bone plasmacytoma only Low M-component production rates IgG <5 g/dL IgA <3 g/dL Urine light chain M component on electrophoresis <4 g/24 hours	< 0.6 (low)
<b>Stage II</b> Fitting neither stage I or III	0.6–1.2 (intermediate)
<b>Stage III</b> One or more of the following Hemoglobin <8.5 g/dL Serum calcium >12 mg/dL Advanced lytic bone lesions High M-component rates IgG >7 g/dL IgA >5 g/dL Urine light chain M component on electrophoresis >12 g/24 hours	> 1.2 (high)
<b>Subclassification</b> A: Serum creatinine <2 mg/dL B: Serum creatinine $\geq$ 2 mg/dL	

<sup>a</sup> Scale of bone lesions: normal bones, 0; osteoporosis, 1; lytic bone lesions, 2; and extensive skeletal destruction and major fractures, 3. Modified from Durie and Salmon (1975). Copyright © 1975 American Cancer Society. By permission of Wiley-Liss.

### 3.9.1 Individual Prognostic Markers With Standard Intensity Chemotherapy

#### 3.9.1.1 $\beta_2$ -Microglobulin

$\beta_2$ M concentration is the strongest and most reliable prognostic factor for multiple myeloma that is available routinely. It depends not only on tumor burden but also on renal function. Increased  $\beta_2$ M values predict early death (Bataille and Harousseau 1997; Bataille et al. 1992; Greipp et al. 1993). Formulas to correct the  $\beta_2$ M concentration for renal insufficiency have not improved its predictive value; the  $\beta_2$ M value is still prognostic in myeloma patients with normal renal function. The British Medical Research Council has shown that after 2 years of survival, the initial  $\beta_2$ M concentration loses its prognostic value.  $\beta_2$ M value also predicts high-dose therapy outcome (ie, event-free and overall survival) (Hahn et al. 2003).

#### 3.9.1.2 C-reactive Protein

French investigators first showed that C-reactive protein was useful as a univariate and multivariate (Bataille et al. 1992) prognostic marker in multiple myeloma. These findings were substantiated in groups of patients from Mayo Clinic and from ECOG clinical trials (Greipp et al. 1993; Rajkumar and Greipp 1999). C-reactive protein concentration does not appear to be useful as a marker of disease status. C-reactive protein value also predicts high-dose therapy outcome.

#### 3.9.1.3 Lactate Dehydrogenase

Increased lactate dehydrogenase values identify a group of patients with poor prognosis and aggressive disease, sometimes a lymphoma-like disease characterized by tumor masses and retroperitoneal adenopathy with a short clinical course. Fewer than 11% of patients with newly diagnosed myeloma have an increased concentration of lactate dehydrogenase (Kyle et al. 2003), thereby limiting its utility.

#### 3.9.1.4 Bone Marrow Plasma Cell Number and Morphology

The quantity, growth patterns, and morphologic features of bone marrow plasma cells have been evaluated as prognosticators for patients with myeloma with vari-

**Table 3.14.** Prognostic and staging systems in newly diagnosed multiple myeloma patients (prognostic categories defined in patients treated with standard intensity chemotherapy, unless stated otherwise)

Study	Patients no.	Risk or stage	Patients %	Features	Median OS, mo
Durie and Salmon (1975)	150	IA	11	Defined in Table 3.13	61
		IIA & IIB	27		54
		IIIA	50		30
		IIIB	13		15
Medical Research Council's Working Party on Leukaemia in Adults (1980)	485	Low	22	BUN ≤8 mM and Hb > 10 g/dL	>48
		Intermediate	56	Not meeting other criteria	~ 34
		High	22	BUN >10 mM and Hb ≤7.5 g/dL	~ 24
Bartl et al., 1987	674	Low grade	71	Marschalko and small PC <sup>a</sup>	40
		Intermediate grade	28	Cleaved, polymorphous asynchronous PC	20
		High grade	2	Plasmablastic PC	8
Bataille et al. (1992)	162	Low	50	$\beta_2M$ and CRP <6 mg/L	54
		Intermediate	35	$\beta_2M$ or CRP ≥6 mg/L	27
		High	15	$\beta_2M$ and CRP ≥6 mg/L	6
Greipp et al. (1993)	107	Low	14	PCLI <1% and $\beta_2M$ <2.7 mg/L	71
		Intermediate	54	PCLI ≥1% or $\beta_2M$ ≥2.7 mg/L	40
		High	32	PCLI ≥1% and $\beta_2M$ ≥2.7 mg/L	17
Finnish Leukaemia Group (1999)	324	I	61	Hb ≥10 g/dL and BMPC <70%	57
		II	25	Hb <10 g/dL or BMPC ≥70%	45
		III	14	Hb <10 g/dL and BMPC ≥70%	25
Konigsberg et al. (2000)	88	Low	36	No FISH del 13q and $\beta_2M$ ≤4 mg/L	102
		Intermediate	40	No FISH del 13q or $\beta_2M$ >4 mg/L	46
		High	24	No FISH del 13q and $\beta_2M$ >4 mg/L	11
Crowley et al. (2001)	1,026	SWOG I	13	$\beta_2M$ <2.5 mg/L	53
		II	43	$\beta_2M$ ≥2.5 but <5.5 mg/L	41
		III	33	$\beta_2M$ ≥5.5 mg/L and alb >3 g/dL	24
		IV	11	$\beta_2M$ ≥5.5 mg/L and alb <3 g/dL	16

Alb, albumin;  $\beta_2M$ ,  $\beta_2$ -microglobulin; BMPC, bone marrow plasma cells; BUN, blood urea nitrogen; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; PC, plasma cells; PCLI, plasma cell labeling index; SWOG, Southwest Oncology Group.

<sup>a</sup> See text for details. The Bartl staging system is a plasma cell morphology-based staging system.

able results (Bartl et al. 1987; Rajkumar and Greipp 1999). Bartl et al. (1987) constructed an intricate study of bone marrow characteristics of myeloma patients. The architectural pattern of growth – including interstitial, interstitial/sheets, interstitial/nodular, nodular,

and packed – correlates with survival, as does the plasma cell morphology. According to these authors, myeloma cell histologic features can be classified into 6 types: 1) Marschalko type – predominantly normal-appearing plasma cells with a mean size of 21 microns; 2) small cell

type – small, round, and lymphoplasmacytoid with mean size of 13 microns; 3) cleaved type – notched, cleaved, or even convoluted nuclei of variable size; 4) polymorphous type – marked cellular polymorphism and multinuclearity, with interspersed giant plasma cells and cytoplasmic inclusions; 5) asynchronous type – marked asynchronous maturation of nucleus and cytoplasm, large eccentric nuclei, frequent nucleoli, and pronounced perinuclear hof; and 6) blastic type – plasmablasts with large nuclei, prominent centrally located nucleoli with a moderate rim of basophilic cytoplasm, and a faint perinuclear hof (Table 3.14). Neither of these morphologic features – architecture or plasma cell histologic features – has been applied widely.

Other investigators have demonstrated the powerful prognostic significance of immature or plasmablastic plasma cells. Plasmablastic morphology is associated with a high PCLI, a higher level of sIL-6R, and *ras* mutations (Rajkumar and Greipp 1999). Electron microscopy confirms that immature nuclear morphology and nuclear cytoplasmic asynchrony correlate with one another and with poor prognosis. Nuclear immaturity and 3 cytoplasmic abnormalities – scattered pattern of mitochondria, single-sac looplike structures, and numerous intramitochondrial granules – have been associated with poor outcome.

### 3.9.1.5 Plasma Cell Labeling Index

The PCLI of the bone marrow plasma cells is a reproducible and powerful prognostic factor in multiple myeloma (Greipp et al. 1993; Rajkumar and Greipp 1999). The PCLI is determined from an immunofluorescence slide-based assay (Greipp et al. 1993). Cells in DNA S phase of the cell cycle incorporate bromodeoxyuridine, which can be recognized by using a monoclonal antibody. S-phase cells are then marked with a second antibody, and plasma cells are recognized by morphology and reactivity with antihuman immunoglobulin kappa and lambda light chain. An increased PCLI predicts short remission and survival but does not predict response to therapy. All large studies published to date have confirmed the independent prognostic value of the PCLI for survival after treatment with conventional chemotherapy (Boccardo et al. 1989; Greipp et al. 1993) or high-dose therapy. Other methods for determining proliferation include Ki67 immunohistochemical staining and determination of S phase by flow cytometry.

### 3.9.1.6 Cytogenetics, Fluorescence In Situ Hybridization, and Other Genetic Abnormalities

Nearly all myeloma patients have abnormal chromosomes by fluorescence in situ hybridization (FISH), including deletions, aneuploidy, and translocations, although abnormal karyotypes are seen in only 18% to 30% of cases. This apparent contradiction is explained by the generally low proliferative rate of myeloma cells and the requirement of obtaining plasma cells in metaphase (and not just the rapidly dividing normal myeloid precursors) to generate conventional cytogenetics (Rajkumar and Greipp 1999). Therefore, any abnormality in conventional cytogenetics identifies a group with a higher proliferative rate and a particularly poor prognosis. There is an excellent correlation between abnormal conventional cytogenetics and high plasma cell proliferative rate (Zojer et al. 2000).

By interphase FISH, aneuploidy is present in the majority of newly diagnosed patients. Aneuploidy is characterized predominantly by a gain of chromosome numbers, but monosomy is not uncommon. With interphase FISH, several chromosomal abnormalities, such as immunoglobulin heavy chain translocations and deletion of chromosome 13, are observed at equal frequencies among the spectrum of plasmaproliferative disorders from MGUS to multiple myeloma to PCL (Avet-Loiseau et al. 2002).

Monoallelic loss of chromosome 13 (del 13) or its long arm (del 13q), when determined by cytogenetics, is a powerful adverse prognostic factor in patients treated with high-dose chemotherapy and hematopoietic stem cell transplantation (Barlogie et al. 1999). Approximately 50% of newly diagnosed multiple myeloma patients have del 13 or del 13q by FISH (Facon et al. 2001; Zojer et al. 2000). Our group has shown that del 13q is associated with specific biologic features, including a higher frequency of  $\lambda$ -type multiple myeloma, slight female predominance, higher PCLI, and higher frequency of serum M component of less than 1 g/dL (Fonseca et al. 2003). Patients with the deletion by FISH have a worse overall survival with standard chemotherapy (Fonseca et al. 2003; Konigsberg et al. 2000; Zojer et al. 2000), high-dose therapy (Facon et al. 2001), and interferon treatment. The absence of abnormalities of chromosome 13 and 11 by conventional cytogenetics is associated with longer complete response duration, event-free survival, and overall survival in patients

treated with high-dose therapy (Barlogie et al. 1999). The prognostic significance of del 13q by FISH is less than that for del 13 by conventional cytogenetics, because the latter test incorporates both the chromosomal abnormality and a high rate of plasma cell proliferation, whereas the former captures only the chromosomal abnormality.

Hypodiploid myeloma has a worse prognosis than diploid or hyperdiploid myeloma. This has been demonstrated by flow cytometric methods and metaphase cytogenetics (Smadja et al. 2001). Controversy exists about whether the deletion 13q adds any additional prognostic information to a hypodiploid karyotype (Smadja et al. 2001).

Up to 75% of patients with multiple myeloma have translocations involving the heavy chain gene on chromosome 14. These translocations include illegitimate switch recombinations of the variable regions of the immunoglobulin heavy chain gene at 14q32. Partners of the translocations into the IgH switch region on chromosome 14 include chromosomes 11, 4, 6, and 16 (Avet-Loiseau et al. 2002). Occurring in 16% of myeloma patients, t(11;14)(q13;q32), which increases expression of cyclin D1, is the most common translocation in multiple myeloma (Avet-Loiseau et al. 2002). Previous publications had suggested that this translocation was associated with an adverse outcome in multiple myeloma (Barlogie et al. 1999; Konigsberg et al. 2000), but more recent data refute this hypothesis. The t(4;14)(p16.3;q32) is present in 10% to 20% of multiple myeloma patients (Avet-Loiseau et al. 2002). This translocation results in the up-regulation of fibroblast growth factor receptor 3 (FGFR3) and in the hybrid transcript IgH/MMSET (Avet-Loiseau et al. 2002). The t(14;16)(q32;q23) is also seen in a small subset (~5%) of patients with multiple myeloma (Fonseca et al. 2003). In one study there was a tight association of del 13 abnormalities and high  $\beta_2$ M values with the unfavorable t(4;14) and t(16;14) abnormalities. The frequency of high  $\beta_2$ M or del 13 was one-half that in patients with the t(11;14) abnormality. This suggests that the poor prognosis associated with del 13 may be because of other nonrandom, associated chromosomal abnormalities. Three distinct staging groups can be defined based on the presence of t(14;16)(q32;q23), t(4;14)(p16.3;q32), deletion 17p13, and del 13q by FISH (Fonseca et al. 2003).

Mutations of *ras* have been noted in 30% to 50% of multiple myeloma patients (Hallek et al. 1998), with increasing prevalence in the advanced stages of the dis-

ease and shorter survival (*K-ras*). Mutations of *ras* were first observed in fulminant disease but have also been observed in 27% to 39% of newly diagnosed cases. Patients with *ras* mutations had a median survival of 2.1 years versus 4 years for patients with wild-type *ras*.

Inactivating mutation of *p53*, locus 17p13, is rare in freshly explanted myeloma cells but is common in human myeloma cell lines and in patients with a terminal phase of myeloma. Such mutations have been observed in ~5% of cases of early multiple myeloma versus 20% to 40% of cases of PCL. Deletions of *p53* as detected by FISH are present in 9% to 33% of patients with newly diagnosed myeloma and confer a poorer median survival (15.9 months versus >38 months).

Epigenetic phenomena, such as methylation of the *p16* (*Met-p16*) promoter region, have been associated with progression in the plasma cell dyscrasias. *Met-p16* is uncommon in MGUS/smoldering multiple myeloma, increases in frequency with advancing stages of the disease, and is common in extramedullary multiple myeloma, including PCL.

### 3.9.1.7 Angiogenesis

Several studies have demonstrated prognostic significance of increased microvessel density (ie, angiogenesis) in multiple myeloma. The first description was a comprehensive study of multiple myeloma and MGUS that showed a strong association with diagnosis and with increased S-phase fraction of plasma cells measured by the PCLI.

### 3.9.1.8 Lymphocyte Subsets

Low numbers of CD4 (helper T) cells at diagnosis are associated with a worse prognosis; the prognostic importance of CD4 T cells is present throughout the course of disease, including after the completion of chemotherapy and at relapse.

In the posttransplantation setting, the number of circulating lymphocytes appears to be an important prognostic factor. Porrata et al. (2001) demonstrated lower relapse rates and prolonged survival for patients with higher absolute lymphocyte counts after autologous stem cell transplantation, suggesting an early graft-versus-tumor effect. The median overall survival and progression-free survival for myeloma patients were significantly longer in patients with an absolute



lymphocyte count  $\geq 500$  cells/ $\mu\text{L}$  on day 15 than for patients with an absolute lymphocyte count  $< 500$  cells/ $\mu\text{L}$  (33 vs. 12 months; 16 vs. 8 months). Desikan et al. at the University of Arkansas made a similar observation. In a trial designed to evaluate the role of more intense conditioning, lymphocyte recovery, evaluated as a surrogate for immune recovery, was inferior in more intensively treated patients. Despite identical complete remission rates, event-free survival and overall survival were significantly decreased among patients receiving more intensive conditioning in 2000.

### 3.9.1.9 Other Prognostic Factors

Other factors that have adverse prognostic value include (Rajkumar and Greipp 1999) decreased staining of bone marrow plasma cells for acid phosphatase; increased circulating plasma cells as measured by the peripheral blood labeling index; apoptotic index; increased sIL-6R; serum neopterin;  $\alpha_1$ -antitrypsin; c-terminal telopeptide of Type I collagen; serum bone sialoprotein; B<sub>12</sub> binding protein; sCD56; soluble Fc receptor (CD16); soluble syndecan or CD138; and serum IL-6 levels. Although IL-6 is known to have a major role in myeloma pathogenesis, C-reactive protein levels correlate well with this more expensive and less readily available prognostic test.

### 3.9.1.10 Drug Resistance

One form of drug resistance is marked by multidrug resistance-1 expression on plasma cells by immunocytochemistry. The presence of this P-glycoprotein in the cell membrane of plasma cells of patients with multiple myeloma is associated with a poor prognosis. Drug resistance measured by immunocytochemical detection of lung resistance protein is highly correlated with failure of response to melphalan and poor subsequent survival.

## 3.9.2 Significance of the Extent of Response After Therapy

### 3.9.2.1 Significance of Response After Standard Intensity Chemotherapy

Response is often used as a measure of efficacy, and it is often assumed that complete remissions are a prerequisite for cure. Indeed, patients treated with standard in-

tensity chemotherapy with responsive disease tend to live a median of 18 months longer than do patients with resistant disease (Bergsagel et al. 1967; Bladé et al. 1994). However, tumor response may speak more to a patient's tumor biology than it does to the therapy in question. Most standard intensity chemotherapy studies suggest that the degree of response does not correlate with survival (Bladé et al. 1994; Oivanen et al. 1999). Rather, the ability to achieve a plateau of at least 6 months' duration is as important, if not more important, as the degree of response to therapy (Corso et al. 1999; Finnish Leukemia Group 1999). The data from only 3 of 27 randomized induction trials would suggest that a higher response rate translates into longer overall survival (Myeloma Trialists' Collaborative Group 1998).

The importance of response kinetics is also a controversial topic. Some data support the premise that those with the most rapid responses with alkylator-based therapy have a shorter remission duration and survival (Belch et al. 1988), and other data contradict this premise (Bladé et al. 1994).

### 3.9.2.2 Significance of a Complete Response After High-Dose Therapy

It is controversial whether the achievement of a complete response, as defined by the disappearance of the M protein by immunofixation of the serum and urine after high-dose therapy with hematopoietic stem cell support, is of prognostic value. Multiple studies have produced inconsistent results (Attal et al. 1996; Bjorkstrand et al. 2001; Davies et al. 2001; Gahrton et al. 1991; Lahuerta et al. 2000). Several of these studies (Attal et al. 1996; Gahrton et al. 1991) did not use the more stringent definition of complete response; they relied on the absence of an M protein on electrophoretic pattern rather than immunofixation negativity. These studies should be interpreted with caution because they do not include several of the most powerful determinants of prognosis – PCLI and conventional cytogenetics (Barlogie et al. 1999; Greipp et al. 1993).

One of these is a retrospective study of 344 patients with multiple myeloma treated with high-dose chemotherapy followed by autologous stem cell transplantation. Patients were not treated uniformly. The 5-year overall survival was 48% in those who had no M protein on immunofixation and 21% in those with a persistent M protein (Lahuerta et al. 2000). In 2001 Alexanian et

al. (Hahn et al. 2003) reported on a series of 68 patients treated with dexamethasone-based induction therapy followed by early high-dose therapy; results were compared to those of 50 patients who were unable to receive high-dose therapy because of socioeconomic reasons. Those patients who achieved immunofixation-negative complete response by either means (ie, high-dose or standard chemotherapy) had a superior overall survival to that of patients who achieved a partial response or less. The implication of these data is that complete response may be an important surrogate marker of long survival and less aggressive myeloma biology. This study was also lacking important baseline prognostic information (ie, PCLI and cytogenetics). In yet another study, Davies and colleagues (2001) reported a series of 96 patients who received high-dose therapy and were assessed for the effect of response on survival. Although there was a trend toward an improved progression-free survival among patients with an immunofixation-negative complete response compared with patients with a partial response (49.4 months vs. 41.1 months,  $P = 0.26$ ), there was no improvement in overall survival. Finally, Rajkumar et al. reported a complete response in 33% of 126 multiple myeloma patients who underwent stem cell transplantation. There was no difference in the overall survival or progression-free survival between patients who achieved a complete response and those who did not; rather, overall survival was significantly influenced by the level of the PCLI.

### 3.9.3 New Staging Systems

Durie-Salmon stage has been the standard of prognosis in multiple myeloma (Durie and Salmon 1975). Deficiencies in this system include the subjectivity of interpretation of the severity of bone lesions and their questionable prognostic value, as well as the limited value of hypercalcemia as a prognostic indicator. Other investigators have designed staging systems (Table 3.14) including other variables:  $\beta_2M$ , C-reactive protein, PCLI, serum albumin, hemoglobin, renal function, del 13q, bone marrow plasma cell involvement, and bone marrow morphology (including plasmablastic morphology) (Bartl et al. 1987; Bataille et al. 1992; Crowley et al. 2001; Facon et al. 2001; Finnish Leukaemia Group 1999; Greipp et al. 1993; Konigsberg et al. 2000; Medical Research Council's Working Party on Leukaemia in Adults 1980). Each of these systems has value, but the goal is to

reach a consensus and to standardize discussions and comparisons among clinical trials and outcomes. An international consensus panel is addressing this.

At Mayo Clinic and ECOG (Greipp et al. 1993), the PCLI is heavily relied on. It has been incorporated into 3 different staging systems. There has been no analysis in which the PCLI was included that it was not one of the most – if not the most – important predictor of survival (Boccardo et al. 1989, Greipp et al. 1993).

Barlogie et al. (1999) proposed a prognostic system for high-dose chemotherapy patients that incorporates “unfavorable cytogenetics” (abnormalities of chromosomes 13 and 11 by conventional cytogenetics) and  $\beta_2M$  values greater than 4 mg/L. The small subset of patients with both unfavorable cytogenetics and increased  $\beta_2M$  values has median event-free and overall survival of only 1.7 and 2.1 years, respectively, compared with 4.2 and 7.0 plus years for patients without unfavorable cytogenetics and any  $\beta_2M$  value. The combination of del 13 by FISH and  $\beta_2M$  was recently proposed as a new staging system in patients receiving high-dose chemotherapy (Facon et al. 2001).

## 3.10 Treatment of Complications and Supportive Care

### 3.10.1 Treatment of Myeloma Bone Disease

Myeloma bone disease is a significant contributor to morbidity. The standard method of following patients is with periodic (every 6 to 12 months) skeletal radiographs; the use of more sophisticated imaging modalities is being explored. Cross-linked N-telopeptides of Type I collagen, which can be measured in the serum or urine, appear to be a sensitive indicator of bone turnover, and urinary levels show a strong positive correlation with the dynamic histomorphometric indices of bone resorption. Despite careful monitoring, patients are at risk for skeletal events.

Monthly intravenous administration of pamidronate has been shown to reduce the likelihood of a skeletal event by almost 50% in patients with multiple myeloma (Berenson et al. 1998). In this study, 392 patients with stage III myeloma and at least 1 lytic lesion received either placebo or pamidronate, 90 mg intravenously administered as a 4-hour infusion monthly for 21 cycles. Skeletal events (pathologic fracture, radiation or surgery, and spinal cord compression) and hypercalcemia

were assessed monthly. The mean number of skeletal events per year was less in the pamidronate group (1.3) than in placebo-treated patients (2.2;  $P=0.008$ ), and the proportion of patients who developed any skeletal event was lower in the pamidronate group ( $P=0.015$ ). A recent study demonstrated equivalency of pamidronate and zoledronic acid (Rosen et al. 2001). Median time to the first skeletal-related event was approximately 1 year in each treatment group, and the proportion of patients with at least 1 skeletal-related event was similar in all treatment groups.

When a lytic bone lesion is present, significant risk factors for fracture of a long bone include increased pain with use and involvement by more than two-thirds the diameter of the bone. These lesions should be treated prophylactically with surgery if they are situated in weight-bearing bones. Endosteal resorption of one-half the cortical width of the femur weakens the bone by 70%. Surgical treatment should be considered for these lesions as well. Once a bone has fractured, healing can occur, especially if proper internal fixation is performed and if patients have an anticipated survival of >6 months. Much of these data regarding malignant bone disease are derived from patients with carcinoma rather than multiple myeloma. In patients with carcinoma metastatic to bone, modest postoperative radiation doses ( $\leq 3,000$  cGy) as adjuvant therapy are associated with better healing, but the role of adjuvant radiation therapy in this setting in multiple myeloma patients is less clear. Multiple myeloma is often chemotherapy sensitive; adjuvant systemic chemotherapy in multiple myeloma patients may be more appropriate than adjuvant radiation therapy. In general, radiation therapy should be used for pain relief in chemotherapy-refractory disease, because it relieves pain in 80% to 90% of patients with bony metastases, long-term in 55% to 70%.

Percutaneous vertebroplasty is occasionally an option for patients with vertebral body compression fracture. Pain relief is generally apparent within 1 to 2 days after injection and persists for at least several months up to several years. Complications are relatively rare, although some studies reported a high incidence of clinically insignificant leakage of bone cement into the paravertebral tissues. Compression of spinal nerve roots or neuralgia due to the leakage of polymer and pulmonary embolism have also been reported.

### 3.10.2 Spinal Cord Compression

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Spinal cord compression, however, remains an important and emergent subject. The usual standard treatment is high-dose corticosteroids and radiation therapy. On rare occasions, surgical decompression may be considered. Because most myelomatous lesions arise from the vertebral body, an anterior surgical approach is generally used, which may contribute to additional morbidity. The 1 small randomized trial addressing the question of radiation versus laminectomy and radiation showed no benefit from laminectomy; similarly, a larger retrospective series found no benefit. If the deficit is due to compression by the plasma cell tumor (rather than a bone fragment retropulsed by a pathologic compression fracture), outcomes with radiation therapy are probably equal to (or superior to) surgical intervention in a radiosensitive tumorlike myeloma.

High-dose corticosteroids may provide immediate pain palliation and improvement in neurologic function. The optimal corticosteroid dose has not been established, but common dose schedules for metastatic disease include dexamethasone in an initial bolus of 10 mg intravenously or 100 mg intravenously followed by 4 mg orally 4 times daily or 100-mg intravenous bolus followed by 96 mg in 4 divided doses for 3 days followed by a dose taper.

### 3.10.3 Hypercalcemia

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Patients with multiple myeloma are at risk for severe hypercalcemia that can precipitate acute renal failure, hypertension, nausea, vomiting, pancreatitis, cardiac arrhythmia, coma, and death. The extracellular volume depletion associated with hypercalcemia should be corrected by vigorous hydration followed by an antiresorptive agent such as intravenous bisphosphonate. Serum calcium value usually declines rapidly, reaching the normal range within 2 to 3 days in more than 80% of cases. It occasionally goes below normal at the nadir. Corticosteroids can also reduce serum calcium concentration in about 60% of patients with hypercalcemia.

Gallium nitrate, mithramycin, and calcitonin are interesting from a historical perspective. Since the advent of bisphosphonates, they are generally not used.

### 3.10.4 Hematologic Complications Including Anemia, Secondary Leukemia, Hyperviscosity, and Cryoglobulinemia

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#### 3.10.4.1 Anemia

The anemia of multiple myeloma can result from many factors. For patients with anemia due solely to myelomatous bone marrow infiltration, chemotherapy remedies the problem. Other patients have a relative erythropoietin deficiency related to renal injury due to the myeloma or to age-related changes. In these patients, as in any patient with renal insufficiency, modest doses of recombinant erythropoietin are effective. For patients with chemotherapy-induced anemia, recombinant erythropoietin may be effective at higher doses (150 to 300 IU/kg thrice weekly or 40,000 units weekly) (Garton et al. 1995). An inappropriately low endogenous erythropoietin concentration is the most important factor predicting response.

#### 3.10.4.2 Secondary Myelodysplasia and Acute Leukemia

The most ominous cause of anemia in the setting of previously treated multiple myeloma is secondary myelodysplastic syndrome or acute leukemia. In the late 1960s and early 1970s investigators noted that cytotoxic agents can induce myelodysplasia and acute myeloid leukemia. The risk of secondary myelodysplastic syndrome or acute leukemia is approximately 3% at 5 years and 10% at 8 to 9 years (Cuzick et al. 1987). The extremes of estimates range from an actuarial risk of 25% at 5 years to 0.7% over 10 years, with multiple other estimates somewhere in between. A reasonable guideline is that the 10-year risk of myelodysplastic syndrome or acute myeloid leukemia is about 3% for every year of melphalan treatment (Cuzick et al. 1987). Some authors have suggested that higher cumulative doses of melphalan are implicated as a risk for acute leukemia; others have shown no difference in incidence based on the number of courses of chemotherapy or the cumulative melphalan dose between the patients who did and did not develop acute leukemia. Investigators from the Finnish Leukaemia Study showed that mean number of chemotherapy cycles was 19.7 and 18.5 in patients with and without secondary leukemia; mean cumulative melphalan doses were 1,440 and 1,400 mg, respectively. Although cyclophosphamide has been shown to be leu-

kemogenic, data suggest that it is less so than melphalan (Cuzick et al. 1987). After secondary leukemia is diagnosed, median survival tends to be short – about 2 months.

The occurrence of multiple cases of acute leukemia in multiple cases of myeloma suggests that there may be a proclivity for acute leukemia to develop in patients with myeloma. After stem cell transplantation for myeloma, the risk of myelodysplastic syndrome appears to be related to prior chemotherapy rather than to the transplant itself, at least in one retrospective series.

#### 3.10.4.3 Cryoglobulinemia

Approximately 5% of myeloma gamma globulins exhibit reversible precipitation in the cold, so-called cryoglobulins, forming either a flocculent precipitate or a gel-like coagulum when the serum is cooled.

#### 3.10.4.4 Hyperviscosity

Plasmapheresis relieves the symptoms of hyperviscosity, but the benefit of this treatment in the absence of concurrent chemotherapy is short-lived.

### 3.10.5 Renal Failure

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A normal creatinine value is present in approximately half of multiple myeloma patients at diagnosis (Kapadia 1980; Kyle et al. 2003). Only 15% to 25% have a creatinine value above 2 mg/dL. If the renal insufficiency reverses, as it does in more than half of cases, survival is 4-fold to 7-fold higher than in those in whom it does not. Factors predicting for renal function recovery include serum creatinine < 4 mg/dL, serum calcium value 11.5 mg/dL, proteinuria < 1 g/24 h, and adequate rehydration. For patients with multiple myeloma and severe renal failure who survive the first 2 months on dialysis, 40% have an objective response to chemotherapy and a median survival of almost 2 years. Factors that increase renal tubular cast formation include dehydration, infection, and hypercalcemia. Maintaining a 24-hour fluid intake of at least 3 liters can improve renal function.

Because light chains with the lowest isoelectric points tend to be more nephrotoxic in animal models, avoidance of a low or acidic urinary pH is recommended. Give either oral or intravenous bicarbonate

in the setting of acute renal failure. The MRC III myelomatosis trial randomized multiple myeloma patients with significant renal failure to oral sodium bicarbonate to neutralize urine pH (or not), and there was a trend toward better survival in the bicarbonate recipients.

The use of plasmapheresis in the setting of renal failure remains controversial. One small randomized study of patients with active myeloma and progressive renal failure suggested benefit of plasmapheresis in a subset of patients (Johnson et al. 1990). Twenty-one patients were randomized to either forced diuresis and chemotherapy (10 patients) or forced diuresis, chemotherapy, and plasmapheresis (11 patients). There was a trend toward better outcome in the plasmapheresis group, but the difference was not statistically significant. It is unclear whether the lack of significance is due to the small sample size (underpowered) or to an equivalence of the 2 therapeutic strategies. The study did demonstrate that the severity of myeloma cast formation directly correlated with lack of improvement regardless of treatment strategy.

### 3.10.6 Infection Management

Infections are a major cause of morbidity in myeloma patients. Pneumonias and urinary tract infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* are most frequent. The susceptibility to infection varies with the phase of illness. In one prospective study, the overall serious infection rate was 0.92 infections per patient-year and was 4 times higher during periods of active disease (1.90) than in plateau phase myeloma (0.49). In a retrospective study evaluating the sequential incidence of infection, the first 2 months of initial chemotherapy emerged as a particularly high-risk period, with nearly half of the patients experiencing at least 1 clinically significant infection. Infections late in the course of multiple myeloma may be an inevitable result of long-standing immunosuppression and overwhelming tumor burden. Prevention of infection is a critical goal for improving survival.

Prevention of infections by use of vaccines is an attractive strategy. Unfortunately, responses to vaccines are poor among myeloma patients. Patients with myeloma were investigated to assess whether immunologic risk factors predisposing to serious infection could be identified. Specific antibody titers to pneumococcal capsular polysaccharides and tetanus and diphtheria

toxoids were significantly reduced compared with the control population. Low antipneumococcal and anti-*Escherichia coli* titers correlated with risk of serious infection. In addition, among 41 immunized patients, responses to pneumococcus vaccine and tetanus and diphtheria toxoids were poor. IgG subclass levels were significantly reduced, and a poor IgG response to pneumococcus vaccine immunization was associated with an increased risk of septicemia. The predominant site of infection was the respiratory tract. Decreased concentrations of the uninvolved immunoglobulins were significantly associated with at least 1 serious infection.

The most common prevention strategy consists of prophylaxis with antibiotics (Oken et al. 1996b). A randomized, placebo-controlled trial of trimethoprim-sulfamethoxazole (TMP-SMX) demonstrated a significant decrease in severe infections among newly diagnosed myeloma patients randomized to TMP-SMX compared with controls (Oken et al. 1996b). Fifty-seven patients about to begin chemotherapy for multiple myeloma were randomly assigned to prophylaxis for 2 months or to no prophylaxis (control). Antibiotic prophylaxis consisted of TMP-SMX (160/800 mg orally every 12 hours) administered for the first 2 months of initial chemotherapy. Bacterial infection occurred in 11 control patients but in only 2 patients assigned to receive TMP-SMX ( $P = 0.004$ ). Eight severe infections occurred in controls compared with 1 in a TMP-SMX patient ( $P = 0.010$ ). Severe infections included 5 cases of pneumonia (3 with sepsis), 2 urinary tract infections with complicating pneumonia or sepsis, 1 diverticulitis with perforation, and 1 staphylococcal scalded skin syndrome. The rate of bacterial infection was 2.43 per patient-year for controls and 0.29 per patient-year for the TMP-SMX group ( $P = 0.001$ ). Toxicity (skin rash in 6 patients, nausea in 1 patient) was not life-threatening but required discontinuation of TMP-SMX in 25% of patients.

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