Multiple Myeloma and Other Plasma Cell Dyscrasias

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This management guide covers the symptoms, diagnosis, screening, staging, and treatment of multiple myeloma, smoldering myeloma, and other plasma cell dyscrasias.

Multiple Myeloma

Multiple myeloma is a disseminated malignancy of monoclonal plasma cells that accounts for 1.3% of all malignancies and 15% of hematologic cancers. The incidence has been increasing by 0.7% each year for the last 10 years while mortality has come down by 1.7% each year over the same period. The incidence rate was 6.1 (7.4 in men and 4.7 in women) and the number of deaths was 3.4 per 100,000 persons per year (4.3 in men and 2.7 in women). Widespread use of the immunomodulatory drugs and proteasome inhibitors over the past decade has resulted in improved life expectancy, with a median survival just under 5 years. The prevalence of multiple myeloma has increased, and currently an estimated 83,367 people in the United States live with myeloma. In 2016, there will be an estimated 30,330 new cases of myeloma, and 12,650 estimated deaths.

Epidemiology

Gender
Men are affected more frequently than women (1.6:1 ratio).

Age
The median age of diagnosis is 69 years, with 75% of diagnosed patients between the ages of 55 and 84.

Race
The annual incidence per 100,000 population, among white men and women, is 7.2 and 4.3, respectively, and among black men and women, 14.8 and 10.5, respectively. This racial difference is not explained by socioeconomic or environmental factors and is presumably due to unknown genetic factors.

Geography
There is no clear geographic distribution of multiple myeloma. In Europe, the highest rates are noted in the Nordic countries, the United Kingdom, Switzerland, Spain, Greece, Italy, Ireland, and Israel. France, Germany, Austria, and Slovenia have a lower incidence, and developing countries have the lowest incidence. This higher relative incidence in more developed countries probably results from the combination of a longer life expectancy and more frequent medical surveillance, although other factors may be involved.

Survival
Relative survival rate measures the survival of cancer patients in comparison to the general population, to estimate the effect of the cancer in question. There has been improvement in the 5-year relative survival rate for patients with multiple myeloma, from 29% in 1990 to 45% in 2009. There has been improvement in survival in all age groups, with median survival estimates now between 5 and 7 years, and more recent data suggesting 7 to 10 years overall survival is achieved in patients receiving novel therapies both as part of initial therapy and at relapse.

Etiology and Risk Factors
No predisposing factors for the development of multiple myeloma have been confirmed, although possible contributing causes include certain toxic exposures and potential underlying genetic vulnerability.
Environment

Some causative factors that have been suggested include radiation exposure (radiologists and radium dial workers), occupational exposure (agricultural, chemical, metallurgical, rubber plant, pulp, wood and paper workers [including carpenters and furniture makers], and leather tanners), and chemical exposure to formaldehyde, epichlorohydrin, Agent Orange, hair dyes, paint sprays, and asbestos. None of these associations has proven to be highly statistically significant, and some have been contradicted by negative correlations. The initial report that survivors of the atomic bombings in Japan had an increased risk of developing myeloma has been refuted by longer follow-up, although the underlying rate of myeloma in the Japanese population is relatively low compared to other countries, and is now increasing.

Viruses

A preliminary report in a limited number of patients noted the presence of herpesvirus 8 in the dendritic cells of patients with multiple myeloma. However, further evaluation by a number of investigators has failed to confirm this result.

Cytogenetics

One of the two primary genetic events, either hyperdiploidy or aberrant class switch recombination (CSR), occurring in antigen-selected post-germinal center B-cells ultimately leads to the development of multiple myeloma. The aberrant CSR results in a nonfunctional immunoglobulin heavy chain gene at 14q32 involved in translocation with partner chromosomes 4, 6, 8, 11, 16, and 20 (Table 1). Translocations involving chromosomes 4, 14, and 16 as well as secondary genetic events such as del17p13 or amplification of 1q21 are associated with poor prognosis. Hyperdiploidy generally consists of trisomies of chromosomes, 3, 5, 7, 9, 11, 15, 19, and 21. Multiple myeloma presents with multiple subclones at diagnosis, which have been shown to appear and disappear with treatment over the course of the disease and account for the ultimate failure to eradicate the disease. Better understanding of the biology of multiple myeloma is underway with the use of whole-genome sequencing, exon sequencing, RNA sequencing, studies of aberrant microRNA expression, and gene expression profiling. Such studies may ultimately help in tailoring therapy in the near future and so better characterize the phenomenon of clonal heterogeneity, as well as the challenging phenomenology of clonal tides, which likely represent the complex integrity of genotypic, phenotypic, and microenvironmental factors.

![Table 1](https://example.com/table1.png)

**Table 1:**

| Oncogenes involved in multiple myeloma, and their locations |

Genetic factors

Multiple myeloma is not an inherited disease, but there have been numerous reports of multiple cases in the same family. However, a case-control study revealed no significant increase in its incidence among relatives of patients who had multiple myeloma, other hematologic malignancies, or other cancers. Nonetheless, this remains an area of active investigation, as case studies continue to describe associations both within families and with certain other cancers, such as renal cell carcinoma.

Pathophysiology

Interactions between multiple myeloma cells and their microenvironment (the extracellular matrix and the bone marrow stroma) allow multiple myeloma cells to survive, grow, migrate, and resist apoptosis induced by traditional chemotherapies. These effects are partially mediated through adhesion-mediated signalling and partly through various cytokines, including IL-6, vascular endothelial growth factor, insulin-like growth factor 1 (IGF-1), and tumor necrosis factor (TNF)-α. The molecular signals mediating the proliferative effects include the RAS/RAF/mitogen-activated protein kinase (MAPK) pathway, whereas the phosphoinositide 3-kinase (PI3K/AKT) pathway provides cell survival and drug resistance signals. Improved understanding of these interactions and the molecular mechanisms mediating them has allowed the evaluation of novel therapies that directly
target multiple myeloma cells as well as act on the bone marrow microenvironment and other milieus, including cortical bone.

**Monoclonal gammopathy of unknown significance (MGUS)**

Patients with MGUS develop myeloma, lymphoma, or amyloidosis at a rate of 1% per year. Recent studies indicate that the diagnosis of symptomatic multiple myeloma is typically preceded by monoclonal gammopathy for 2 or more years.

**Signs and Symptoms**

The clinical features of multiple myeloma are variable. Findings that suggest the diagnosis include lytic bone lesions, anemia, azotemia, hypercalcemia, and recurrent infections. Approximately 30% of patients are free of symptoms and are diagnosed on routine physicals with abnormal laboratory studies, including elevation of serum protein.

**Bone disease**

Bone pain, especially from compression fractures of the vertebrae or ribs, is the most common symptom. At diagnosis, 70% of patients have lytic lesions, which are due to accelerated bone resorption. These changes are due to pathological imbalance between osteoblast (bone formation) and osteoclast (bone resorption) activity in the bone marrow microenvironment, induced by the presence of myeloma cells. Factors inducing osteoclastic activity include interleukin (IL)-1beta, TNF-α, and IL-6, as well as newly identified factors such as osteoprotogerin, TNF-related activation-induced cytokine (TRANCE), macrophage inflammatory protein (MIP)-1α, and receptor activator of nuclear factor kappa B (RANK) ligand. Osteoblastic activity is inhibited due to production of a soluble factor Dickkopf homolog 1 (DKK-1) by multiple myeloma cells, and overexpression of Activin-A by bone marrow stromal cells.

**Anemia**

Normocytic, normochromic anemia is present in 60% of patients at diagnosis. It is due primarily to the decreased production of red blood cells by marrow, infiltration with plasma cells, and the suppressive effect of various cytokines. Patients with renal failure may also have decreased levels of erythropoietin, which can worsen the degree of anemia.

**Hypercalcemia**

Among newly diagnosed patients, up to 20% have hypercalcemia (corrected serum calcium level > 11.5 mg/dL) secondary to progressive bone destruction, which may be exacerbated by prolonged immobility, especially in the context of fracture. Hypercalcemia should be suspected in patients with myeloma who have nausea, fatigue, confusion, polyuria, or constipation. It may also suggest high tumor burden. It should be considered an oncologic emergency and requires prompt treatment with aggressive hydration, use of bisphosphonates, calcitonin, and antimyeloma therapy, including steroids.

**Renal failure**

Approximately 20% of patients present with renal insufficiency and at least another 20% to 40% develop this complication in later phases of the disease. Light-chain cast nephropathy is the most common cause of renal failure. Additional causes include hypercalcemia, dehydration, and hyperuricemia. Less commonly, amyloidosis, light-chain deposition disease, nonsteroidal anti-inflammatory agents taken for pain control, intravenous radiographic contrast administration, and calcium stones may contribute to renal failure. More recently, bisphosphonate therapy has been associated with azotemia, which is usually reversible with treatment cessation.

**Infections**

Many patients with myeloma develop bacterial infections that may be serious, and infectious complications remain the most common cause of death in myeloma patients. In the past, gram-positive organisms (eg, *Streptococcus pneumoniae, Staphylococcus aureus*) and *Haemophilus influenzae* were the most common pathogens. More recently, however, infections with gram-negative organisms, anaerobes, and fungi have become frequent. The increased susceptibility of patients with multiple myeloma to bacterial infections, specifically with encapsulated organisms, has been attributed to impairments of host-defense mechanisms (such as hypogammaglobulinemia, qualitative deficiency in immunoglobulin function, granulocytopenia, decreased cell-mediated immunity) and the prolonged use of steroids.
Screening and Diagnosis

No screening measures for multiple myeloma have demonstrated any benefit to date.

### TABLE 2: Common laboratory features of plasma cell dyscrasias

The diagnosis usually requires the presence of bone marrow plasmacytosis and a monoclonal protein in the urine and/or serum (Table 2), along with end-organ damage. One immunoglobulin class is produced in excess, whereas the other classes are usually depressed, with all three heavy chains typically reduced in the presence of light chain disease.

**Initial workup**

The initial workup for patients suspected of having a plasma cell dyscrasia should include:
- CBC with differential count and platelet count
- Routine serum chemistry panel (to include calcium, blood urea nitrogen, creatinine)
- Bone marrow aspirate and biopsy to assess clonal plasmacytosis
- Serum protein electrophoresis and immunofixation to quantitate and define protein type
- Serum beta-2-microglobulin, serum albumin
- Serum free light chain
- 24-Hour urine protein, electrophoresis, and immunofixation
- Quantitative serum immunoglobulin levels
- Skeletal survey (bone scans contribute little since isotope uptake is often low in purely lytic bone disease)
- Cytogenetics, including FISH (fluorescence in situ hybridization) on bone marrow plasma cells.

The recently available serum free light chain assay is useful especially in patients with light-chain-only disease, oligo- or nonsecretory myeloma, renal failure, and amyloidosis. MRI is an excellent tool for evaluation of spinal cord compression/impingement. In addition, MRI identifies generalized marrow signal abnormalities and focal lesions that can be monitored after therapy. Whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan provides details of axial and appendicular skeletal involvement but also identifies extramedullary soft-tissue plasmacytomas presenting as macrofocal lesions. Both MRI and PET/CT are especially useful in staging oligo- or nonsecretory disease. Additional useful data may be obtained by analysis of such prognostic factors as plasma cell labeling index, ploidy, immunophenotyping, flow cytometry, C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels.

**Laboratory and Pathologic Features**

**Peripheral blood**

The peripheral blood smear may reveal a normocytic, normochromic anemia with rouleaux formation. Less commonly, circulating plasma cells may also be seen.

**Bone marrow**

Bone marrow examination usually reveals an increased number of plasma cells. These cells are strongly positive for CD38, CD138, MUM1, SLAMF7, and a single class of cytoplasmic immunoglobulin (cIg). The majority of myeloma cells also express CD40 and CD56. Myeloma cells are negative for CD5, CD19, and surface Ig (sIg) expression. CD20 may be expressed in a subset of myeloma patients presenting with the t(11;14) translocation. CD10 expression is generally negative but has sometimes been noted in advanced disease. Monoclonality is frequently demonstrated by immunoperoxidase staining with κ and λ antibodies. The pattern of bone marrow involvement in plasma cell myeloma may be macrofocal. As a result, plasma cell count may be normal when an aspirate misses the focal aggregates of plasma cells that are better visualized radiographically or on direct needle biopsy, where the degree of plasmacytosis will be commensurably high.
Monoclonal proteins

The types of monoclonal protein produced are IgG (60%), IgA (20%), IgD (2%), IgE (< 0.1%), or light-chain κ or λ only (18%). IgM myeloma is rare, but distinct from its lymphoplasmacytic counterpart, Waldenström’s macroglobulinemia. Biclonal elevations of myeloma proteins occur in < 1% of patients, and < 5% of patients are considered to have nonsecretory disease, because their plasma cells do not secrete detectable levels of monoclonal Ig.

Staging and Prognosis

Patients with symptomatic myeloma should be staged using either the Durie-Salmon system at diagnosis or the International Staging System (ISS), which is determined at the time systemic therapy is begun. These two systems are compared in Table 3. The Durie-Salmon staging system better provides information on tumor burden, whereas the ISS better serves as a prognostic indicator. The ISS is easier to use, and it classifies patients correctly regardless of their geographic origin (ie, North America, Europe, or Asia), age (ie, ≥ 65 years vs younger age), or type of treatment (ie, conventional chemotherapy vs high-dose therapy followed by autologous stem cell transplantation). More recent studies have provided evidence that the ISS is also reliable in patients treated with thalidomide (Thalomid), bortezomib, or lenalidomide, and has prognostic value at relapse.

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<th>TABLE 3: The Durie-Salmon system and the International Staging System for multiple myeloma</th>
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Prognosis

Prognostic indicators may help guide treatment strategy, but the presence of poor prognostic features also should not result in initiation of therapy in patients with asymptomatic myeloma, although they should engender caution. Prognostic factors for risk stratification are well established for conventional chemotherapy. Use of bortezomib and, to some extent, lenalidomide may be able to overcome some features of poor risk, including adverse cytogenetics.

**Cytogenetic abnormalities.** Cytogenetic abnormalities detected by conventional karyotyping, such as hyperdiploidy, hypodiploidy or translocations, and deletions and presence of marker chromosomes are associated with adverse outcome. Primary translocations involving 14q32 and 4p16 (fibroblast growth factor receptor 3 [FGFR3]), 16q23 (c-maf proto-oncogene), and del17p13 (TP53) or amplification of 1q21 detected by FISH in multivariate analysis have been shown to be important predictors of poor survival. These cryptic translocations are best detected using FISH, which has been shown to be prognostically useful to evaluate patients both at diagnosis and at relapse.

**Beta-2-microglobulin.** Serum beta-2-microglobulin level is an important prognostic indicator, is integral to the ISS, and in combination with cytogenetics (including FISH) has strong predictive value. As beta-2-microglobulin is excreted by the kidneys, high levels are observed in patients with renal failure; even in this setting, elevated serum beta-2 microglobulin is associated with poor outcome.

**LDH.** High LDH levels also have been associated with plasmablastic disease, extramedullary tumor, plasma cell leukemia, plasma cell hypodiploidy, drug resistance, and shortened survival.

**Other indicators.** Other indicators of shortened survival include elevated CRP, DNA hypodiploidy, high plasma cell labeling indices, and plasmablastic histology. Patients with DNA hypodiploidy are also less likely to respond to conventional chemotherapy. Finally, extramedullary disease is associated with worse outcome, especially in the context of a large tumor burden such as bone involvement and bulk disease.
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Treatment Response Criteria

Because the criteria for treatment response in patients with multiple myeloma have varied among institutions and evolved over time, response rates have been difficult to compare in the past. In responders, the Bence-Jones protein level is reduced more rapidly than is serum myeloma protein, because of the rapid renal clearance of light chains. The Center for International Bone Marrow Transplant Registry/European Bone Marrow Transplant Registry (CIBMTR/EBMTR) response criteria have been prospectively validated in numerous studies and are as follows:

Complete response (CR) requires all of the following:
- No serum/urate M protein by immunofixation electrophoresis for ≥ 6 weeks
- < 5% plasma cells in bone marrow aspirate
- No increase in the size or number of lytic bone lesions
- Disappearance of soft-tissue plasmacytomas.

Partial response requires all of the following:
- ≥ 50% reduction in serum M protein > 6 weeks
- ≥ 90% reduction in 24-hour urinary light-chain excretion
- ≥ 50% reduction in soft-tissue plasmacytomas.

Minimal response (but ≤ 49%) requires:
- ≥ 25% reduction in serum M protein for > 6 weeks
- ≥ 50%-89% reduction in 24-hour urinary light-chain excretion
- No increase in the size or number of lytic bone lesions.

The more recent Uniform Criteria for response proposed by the International Myeloma Working Group (IMWG) have sought to further refine these criteria by describing a stringent CR and a very good partial response (VGPR; > 90% reduction in the serum paraprotein level), as well as defining progressive disease in terms of minimum requirements of paraprotein increase, as opposed to changes in immunofixation alone. Near complete response is another modification of the criteria and has been applied to the EBMTR as part of a number of prospective studies.

Treatment

Exciting advances in the understanding of tumor biology and microenvironment—and their potential interaction—have helped to identify unique targets for rational therapeutic intervention to enhance outcome, which has not improved with conventional chemotherapy over the past 3 decades. Until recently, only 5% to 10% of patients with multiple myeloma lived longer than 10 years. While survival has improved dramatically with the introduction of novel therapies, cure remains elusive and the outcome for relapsed and refractory patients is dismal.

Newly diagnosed patients

The goal of first-line therapy for myeloma is to obtain the maximum tumor cytoreduction and maintain the remission as long as possible. This is accomplished by combination chemotherapy over a period of 9 to 12 months to obtain maximum tumor cytoreduction. In younger, willing, and fit patients, chemotherapy is followed by high-dose melphalan and autologous stem cell rescue as a consolidation treatment, to induce longer, deeper remission and prolong life expectancy. After maximum tumor cytoreduction with initial therapy and/or stem cell transplantation, the patient may be offered maintenance therapy.

Chemotherapy.

• Dexamethasone/thalidomide—Thalidomide (defined as an immunomodulatory drug [IMiD] and the first in its class to be tested clinically) has been employed alone and in combination with dexamethasone as initial therapy in newly diagnosed patients. When employed alone, response (50% reduction in paraprotein) was observed in 36% of patients; when it was used along with dexamethasone, the response rate was higher (72% and 64% in two studies), including a 16% CR rate in one study.

Thalidomide and dexamethasone in combination is now a less popular induction therapy for newly diagnosed symptomatic myeloma patients. However, this regimen is clearly superior to vincristine, doxorubicin, and dexamethasone (VAD) chemotherapy as a pretransplant regimen and the use of melphalan (Alkeran) and prednisone (MP) for transplant-ineligible patients, with the latter two regimens considered obsolete. Current preferred use of thalidomide would be as a third agent in combination with bortezomib and dexamethasone (VTD) or cyclophosphamide, and with
dexamethasone (CTD) or melphalan and prednisone (MPT). Adequate attention and preventive measures are required for constipation, deep vein thrombosis (DVT), bradycardia, and peripheral neuropathy.

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<th>TABLE 4: Proposed initial treatments for multiple myeloma</th>
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- **Pulse dexamethasone alone**—Pulse dexamethasone administered alone as initial therapy is no longer recommended. However, brief therapy with pulse dexamethasone may be warranted under special clinical circumstances (e.g., renal failure, hypercalcemia, cord compromise requiring radiation therapy, cytopenia) (Table 4).

- **MP**—The combination of melphalan and prednisone has been used over the past 40 years, and other combinations of multiple alkylating agents have not been found to be superior to MP. Approximately 40% of patients respond to the MP regimen, with a median remission duration of 18 months and an overall median survival of 3 years. The MP regimen should be avoided in patients considered to be transplant candidates. Currently, MP should be combined with a novel agent, such as thalidomide, bortezomib, or lenalidomide, as described below.

- **MP and thalidomide (MPT)**—In two large, prospective, randomized trials in patients older than 65, and a third randomized trial in patients over 75 years of age, MPT has been shown to be superior to MP for response rate as well as progression-free survival and overall survival. Side effects (including constipation, DVT, and peripheral neuropathy) were more commonly encountered with thalidomide but were found to be manageable. MPT offers a possible alternative for older people who generally are not candidates for high-dose therapy.

- **MP and Velcade (bortezomib; MPV)**—Bortezomib is a first-in-class, potent, selective, and reversible small-molecule inhibitor of the proteasome. In a large, international, randomized clinical trial, MPV was shown to be superior to MP for response as well as survival endpoints. MPV induced complete remissions in one-third of the patients, with an ORR of 71% and a 2-year overall survival of > 80%. Such high CRs previously were never seen in this population of patients, where one-third of the patients were over age 75 years. Adverse side effects (e.g., peripheral neuropathy, asthenia, fatigue, diarrhea, and constipation) were more frequently encountered on the bortezomib arm. However, the treatment was well tolerated by most patients, with treatment discontinuation due to toxicity noted in only 14% of patients in both arms, and a treatment-related mortality of 1% with MPV (vs 2% in the MP group).

Two large randomized trials support the use of weekly bortezomib to reduce the adverse side effects, especially neuropathy, without compromising efficacy. Furthermore, subcutaneous administration of bortezomib has improved the tolerance of this agent and reduced its toxicity, especially neuropathy, although this approach in combination requires further study.

- **Rd (lenalidomide and dexamethasone)**—Lenalidomide and weekly dexamethasone alone or in combination with clarithromycin have been shown to be an active induction regimen regardless of whether the patient is considered eligible for high-dose therapy and stem cell transplantation. Three-year overall survival estimates are approximately 80% in studies to date. Generally, stem cell harvest is recommended after exposure to 4–6 cycles of treatment to avoid compromising stem cell yield. Chemotherapy-based mobilization (such as with high-dose cyclophosphamide) or use of plerixafor (Mozobil) is recommended. The FIRST trial was a pivotal study that established lenalidomide and weekly dexamethasone (Rd)
administered continuously until progression as the standard of care for patients not undergoing high-dose therapy consolidation. The FIRST trial, a multicentric open-labeled randomized phase III trial has compared Rd continuously until progression (Rd-c) to 72 weeks of Rd (Rd-18) or melphalan prednisone thalidomide (MPT). It showed that Rd-c was well tolerated even in patients over 75 years of age, and was associated with significantly better outcome based on progression-free survival and overall survival, respectively—42% at 3 years and 59.4% at 4 years. The ORR was 75% and the CR rate was about 15%. Rd induction was also noted to be as good as MPR or CRP induction therapy; however, the use of melphalan was associated with more cytopenia. Adverse events with Rd include low blood counts, skin rash, infection, and DVT. DVT prophylaxis is mandatory and aspirin, warfarin, or enoxaparin is employed, depending on additional risk and comorbidities. Peripheral neuropathy is less common. Lenalidomide used in combination with a once-weekly dose of dexamethasone (Rd) should be preferred to its use with more intensive dexamethasone (RD) as the latter was associated with increased risk of thrombocytic events, infections, and early death.

Lenalidomide and weekly dexamethasone is also an acceptable induction therapy for younger patients considering high-dose therapy and stem cell transplant. However, transplant-eligible patients should not be exposed to more than 3 to 6 months of lenalidomide prior to stem cell harvest. Lenalidomide, like melphalan, does impede stem cell mobilization with more extensive exposure.

Pretransplant induction. Pretransplant induction chemotherapy is generally brief, consisting of 3 to 6 cycles of combination chemotherapy. Many different combinations have been used successfully as noted below. In a large randomized trial, bortezomib-containing combinations have shown greater antitumor response compared to conventional chemotherapy.

- **MPR**—Lenalidomide can be added to melphalan and prednisone, but a dose reduction of melphalan and lenalidomide is required. An international randomized clinical trial has shown that melphalan and prednisone is equivalent to melphalan, prednisone, and lenalidomide given for 9 months, but if the melphalan–prednisone combination was followed by lenalidomide maintenance, the progression-free survival improved by almost a year and a half compared with progression-free survival in populations who were unmaintained.

### Treatment options for multiple myeloma

- **Bortezomib and dexamethasone (VD)**—Addition of bortezomib to the induction regimen has substantially improved patient outcomes, especially for patients with adverse genetic risk factors. Randomized phase III trials have shown bortezomib combinations (bortezomib and dexamethasone [VD]; bortezomib, adriamycin, and dexamethasone [PAD]; bortezomib, thalidomide, and dexamethasone [VTD]) to be superior to the VAD induction regimen; bortezomib–dexamethasone significantly improved post-induction and post-transplantation complete response, yielded very good partial response rates compared with VAD, and resulted in a trend toward longer progression-free survival and overall survival. The combination of bortezomib, lenalidomide, and dexamethasone (VRD) is well tolerated and yields the highest overall CR rate and a VGPR rate comparable to that of any regimen used to date without transplantation in the newly diagnosed setting. Other promising regimens include cyclophosphamide, bortezomib, and dexamethasone (CyBORD) as well as the combination of carfilzomib (a recently approved second-generation proteasome inhibitor indicated for use in the relapsed setting) with lenalidomide and dexamethasone (CRd).

- **Bortezomib/lenalidomide/dexamethasone (VRD)**—Two phase II studies have shown a greater depth of response to induction therapy with VRD, with an ORR around 75% and a VGPR+CR rate from 11%
to 32% after 4 cycles. Side effects include peripheral neuropathy (17% grade 3 in the EVOLUTION study). DVT and herpes zoster virus (HZV) prophylaxis are mandated. Phase III trials using bortezomib, lenalidomide, and dexamethasone are ongoing and will help to define the role of lenalidomide in association with bortezomib and dexamethasone compared with bortezomib/dexamethasone alone or lenalidomide/dexamethasone alone. Addition of a fourth agent (liposomal doxorubicin, cyclophosphamide) has not improved the response rate but has added to treatment toxicity.

- **Bortezomib/cyclophosphamide/dexamethasone (CyBorD or VCD)**—Two phase II trials have shown the efficacy of the combination of bortezomib, cyclophosphamide, and dexamethasone to be comparable to that of VRD. The ORR was over 80% to 90%, with VGPR or better seen in 50% to 60% of patients. The major toxicity was hematologic. This combination is particularly well suited for patients with renal impairment.

- **Bortezomib/thalidomide/dexamethasone (VTD)**—Three phase III trials have shown the combination of VTD to induce a high response rate, superior to that associated with thalidomide-dexamethasone or bortezomib plus combination chemotherapy (VBMCP/VBAP). Induction therapy of 3 to 6 months induces a VGPR or better in over 50% to 60% of patients and an ORR of 85% or better. Grade 3 or greater neuropathy occurs in 10% to 15% of patients treated with full-dose bortezomib. Cyclophosphamide can be added to the regimen. This combination is well suited for patients with renal impairment.

- **Bortezomib/doxorubicin/dexamethasone (PAD)**—PAD superiority over VAD induction was demonstrated in a phase III trial. The ORR reported was 78% with a VGPR-or-better rate exceeding 40%. PAD induction was associated with more gastrointestinal symptoms, peripheral neuropathy, HZV, or thrombocytopenia. However, patients with renal impairment benefited from this regimen.

- **Carfilzomib-containing triplet regimen**—Phase II trials have demonstrated the safety and efficacy of carfilzomib-containing regimens for induction. In combination with immunomodulatory drugs (thalidomide or lenalidomide) or cyclophosphamide, an ORR over 90% to 95% has been reported with a VGPR or better seen in 64% with CarTD, 65% with CarCD, and 85% with CarRD. Good results were also seen with CarMP. All combinations are well tolerated, and suitable for elderly patients. Side effects include cardiac symptoms, dyspnea, and constitutional symptoms.

- **Cyclophosphamide/thalidomide/dexamethasone (CTD)**—A phase III study of noninferiority between CVAD and CTD has shown an 82.8% ORR and 43% of patients with CR+VGPR response at the end of induction in the CTD arm. Side effects included infection, cytopenia, somnolence, and constipation. CTD with dose adjustment for elderly patients in the MRC Myeloma IX trial has been associated with better depth of response, showing an ORR of 64%, which is almost twice the ORR obtained with MP, and a CR rate of 13%. Despite those results, it was not correlated with an improvement in progression-free survival or overall survival. Contrary to results with other thalidomide-based regimens, overall survival was low, with a median overall survival of 33.2 months. Side effects encountered included peripheral neuropathy and motor neuropathy, thromboembolic events, and infections.

- **Cyclophosphamide/lenalidomide/dexamethasone (CRD)**—Cyclophosphamide added to bortezomib and dexamethasone has shown promising results. One phase II trial showed a good response to administration of CRD. One advantage of this regimen was the low rate of neuropathy, similar to what has been described with VCD. However, a high rate of cytopenia, especially neutropenia (seen in 60% of patients), and a 25% rate of harvest failure on GCSF (granulocyte colony-stimulating factor) alone offset the positive response to this regimen. The ORR was 79% after 4 cycles, with a VGPR+CR rate of 30%.

- **Melphalan/prednisone/thalidomide (MPT)**—Melphalan-prednisone (MP) has been used as a standard of care for elderly people for many years. The addition of thalidomide has demonstrated an improvement in the outcome. A meta-analysis of the six trials found MPT increased the ORR; improved progression-free survival, with a benefit of 5.6 months; and improved overall survival, with a 6.6-month benefit. During the first year of treatment, however, a higher mortality was seen with this regimen. Side effects from thalidomide include peripheral neuropathy, DVT, constipation, asthenia, bradycardia, and infection. DVT prophylaxis is recommended.

- **Melphalan/prednisone/Velcade (bortezomib; MPV)**—The VISTA trial established MPV to be superior to MP for patients ineligible for high-dose therapy. The ORR was twice the ORR observed with MP, and one-third of the patients achieved a complete remission. There was a benefit shown in the time to progression (with a median of 2 years for VMP group) and in the overall survival (46% of the patients were alive at 5 years). Use of velcade was associated with more adverse side effects, such as peripheral neuropathy, asthenia, diarrhea, constipation, and HZV. However, the rate of treatment
discontinuation due to toxicity was the same in both groups. Side effects, especially neuropathy, can be mitigated without loss of efficacy by administering bortezomib subcutaneously once weekly.

• **Melphalan/lenalidomide/prednisone (MPR)**—Two phase III trials have documented the outcome of this regimen using reduced doses of lenalidomide. MPR showed an ORR of about 70%, with a rate of VGPR or better around 30%. In the MM-015 trial, it was compared against both MP and MPR with lenalidomide maintenance (MPR-R). MPR was significantly better than MP in terms of ORR, however it did not yield a better outcome in terms of progression-free survival or overall survival, contrary to MPR-R. Palumbo et al demonstrated that the outcome of treatment with Rd MPR or CRP was statistically no different, with a 2-year progression-free survival of about 50% and a 2-year overall survival of 80%. However, the use of melphalan was significantly associated with more cytopenia, dose reduction, or discontinuation of the drug.

**High-dose therapy following induction therapy.** Consolidation with high-dose therapy after induction therapy improves the response rate as well as event-free survival and overall survival, especially in good-risk patients. Randomized trials from France and the United Kingdom showed improvement in event-free survival and overall survival following high-dose therapy, compared with conventional chemotherapy alone. Induction with novel agents containing bortezomib and lenalidomide followed by high-dose therapy further improved the outcome, with an expected 3-year survival of about 80%. In a randomized trial reported from Italy, induction with VTD, followed by tandem transplantation and then consolidation with VTD followed by steroid maintenance, resulted in a very high CR of 58%, 3-year progression-free survival of 68%, and overall survival of 86%, with clear superiority to thalidomide and dexamethasone (TD) as a comparator. A novel agent induction regimen followed by single transplantation has thus become a new standard of care, with three drugs now generally preferred (eg, the combinations RVD or VTD), especially in high-risk patients. A high-dose alkylating agent, most commonly melphalan at 200 mg/m² with peripheral blood stem cell support, is a standard conditioning regimen. Addition of total-body irradiation (TBI) does not improve the outcome but increases morbidity and results in higher mortality. Interestingly, in a randomized study, Fermard et al have confirmed an equivalent survival benefit between up-front high-dose therapy vs high-dose therapy as a salvage regimen at relapse following initial induction therapy. This concept is being further evaluated in the era of novel therapies, particularly in a series of important ongoing randomized trials.

**High-dose therapy supported by autologous stem cell transplant (HDC/ASCT)**

**Stem cell harvest.**

• **Single transplant**—In the 1990s, two randomized trial groups have demonstrated an improvement in event-free survival and overall survival (with a benefit of 1 year in the MRC [Medical Research Council] Myeloma VII trial) with the use of HDT/ASCT compared with conventional chemotherapy. Newer therapies including proteasome inhibitors (bortezomib) and the immunomodulatory drugs (thalidomide) have subsequently found a place in the induction regimens and have increased the pre-transplant response (see induction treatment). The overall survival reported with VTD followed by a single HDT/ASCT is about 80% at 3 years. Most randomized clinical trials to date show improvement in the depth of response and progression-free survival. One meta-analysis confirmed the progression-free survival benefit, whereas no overall survival benefit was shown. Moreover, the survival benefit is unclear in the era of novel agents and maintenance therapy. Randomized clinical trials are currently underway to address the role of high-dose therapy and stem cell transplant. A high-dose alkylating agent, most commonly melphalan at 200 mg/m² with peripheral blood stem cell support, is a standard conditioning regimen. Addition of total-body irradiation (TBI) does not improve the outcome but increases morbidity and results in higher mortality.

• **Tandem transplants**—The improved outcome reported after tandem transplants in large cohorts of patients in single-institution studies has not been confirmed. Meta-analysis pointed out increased treatment-related mortality and a lack of sufficient information in those trials to draw firm conclusions. In the Intergroupe Francophone du Myélome (IFM) IFM94 randomized study, 11 years after initiation of therapy, there was only a trend in event-free survival and overall survival in favor of tandem transplants. Moreover, the added benefit of the second transplant was not seen in a subset of patients with a CR or a VGPR after the first transplant in either study. With the advent of novel therapies, the use of tandem transplant has undergone re-evaluation, and the need for a second transplant in patients responding to novel agent-based therapy and single transplant appears to have diminished, making this approach less attractive than, for example, a delayed transplant after subsequent relapse.
Recently, trials comparing the use of consolidation chemotherapy (melphalan–prednisone–lenalidomide or cyclophosphamide–lenalidomide–dexamethasone after lenalidomide–dexamethasone induction) versus tandem transplant demonstrated a benefit in progression-free survival from the use of tandem HDC/ASCT, although no overall survival improvement was seen.

Radiotherapy. Higher doses of radiotherapy (40–50 Gy) are employed for local control and cure of solitary plasmacytoma involving bone and extramedullary sites. Lower doses (20–30 Gy) may be employed for palliation of local bone pain from tumor infiltration, pathologic fractures, and spinal cord compression. It should be emphasized that excellent pain relief may be obtained by prompt institution of high-dose corticosteroid therapy, especially in newly diagnosed patients. Radiotherapy should be employed sparingly, as irradiation of multiple sites may impair stem-cell mobilization in patients who are candidates for high-dose therapy. Employment of high doses of radiation to the spine may preclude the subsequent use of TBI as a conditioning regimen for high-dose therapy, although the latter is now rarely used.

Remission maintenance

Maintenance therapy been shown to prolong remission duration after initial treatment with or without high-dose therapy and improve survival, with the use of specific novel agents, namely lenalidomide and bortezomib. It continues to be an area of intense clinical research.

Lenalidomide. The FIRST trial demonstrates that Rd-c offered a 5-month progression-free survival benefit compared with Rd-18. Similarly, in the MM-015 trial, MPR followed by lenalidomide maintenance was associated with a 17-month progression-free survival benefit compared with MPR. Those trials support the use of lenalidomide for maintenance after induction, however no difference in overall survival was reported.

In the post-transplantation setting, IFM 2005-002 and a landmark Cancer and Leukemia Group B (CALGB) study have evaluated the use of lenalidomide as maintenance. These studies have shown improvement in progression-free survival by at least 18 months for lenalidomide maintenance compared with placebo. The CALGB trial also demonstrated an overall survival benefit. In the IFM study, recent data after a median follow-up of 77 months still showed no survival benefit; this is because of better second progression-free survival in the placebo group. There was an increased incidence of second primary malignancy in the lenalidomide maintenance arms in these studies (8% and 13%), with a small effect on the occurrence of various solid tumors and hematologic malignancies, including myelodysplastic syndrome and acute myeloid leukemia post HDC/SCT apparent with current follow-up. Currently it appears that the risk of relapse and death from myeloma far outweighs the risk of dying from a second primary malignancy. When lenalidomide maintenance is recommended following a melphalan-based regimen, careful observation is recommended and the patient should be counseled appropriately regarding these potential risks, with a maintenance duration of 2 years recommended. The duration of maintenance therapy remains a question (limited duration vs until progression). In the IFM study, lenalinomide was discontinued after 24 months; however, there was still a progression-free survival benefit for patients who had received lenalidomide.

A recent European Myeloma Network trial has also compared the benefit of introducing prednisone along with lenalidomide (RP). Although discontinuation of the steroid is currently preferred with long-term treatment, this trial showed a progression-free survival benefit to treatment with RP. Moreover, the toxicity was equivalent and rash was observed less often in the RP arm.

Thalidomide. Six large phase III trials have reported a benefit in progression-free survival with thalidomide, while only two reported an overall survival benefit from thalidomide maintenance following high-dose melphalan therapy with autologous stem cell transplant (HDM/ASCT). Similar results were seen in patients who were not undergoing transplant. Overall, meta-analysis confirmed an improvement in survival (progression-free survival and overall survival). However, tolerability of the drug remains a challenge based on the high rate of therapy discontinuation, related mainly to neuropathy. Of note, the MRC Myeloma IX Trial showed that thalidomide maintenance was associated with worse survival for patients with high-risk genetics as determined by FISH.

Bortezomib. Two phase III trials have compared in transplant-eligible patients the contribution of bortezomib maintenance. The HOVON study compared bortezomib received in induction and maintenance therapy to a conventional induction therapy with thalidomide maintenance. Bortezomib was associated with a significant improvement in terms of progression-free survival and overall survival. Notably, patients with renal impairment and in the high-risk group (based on ISS and cytogenetics) seemed to benefit from bortezomib. Another PETHEMA trial reported a significant
improvement in progression-free survival with bortezomib–thalidomide maintenance compared with thalidomide alone after ASCT. In another study by the Spanish myeloma group following a bortezomib-based induction regimen for patients ineligible for transplantation, maintenance with bortezomib–thalidomide was shown to be superior to bortezomib–prednisone, and a study from the Italian myeloma group showed a survival benefit with bortezomib and thalidomide compared with observation alone, however the induction therapies were different.

Bortezomib as maintenance therapy is, however, associated with neuropathy, which is often responsible for treatment discontinuation. The use of subcutaneous and oral forms is being evaluated.

**Interferon-α.** Twenty-four randomized trials have investigated interferon-α as maintenance therapy, and neither consistent nor significant benefits have been seen. A large Intergroup trial also reported no benefit of interferon maintenance therapy after conventional therapy and autotransplantation. Side effects, including fatigue and depression, have seriously limited the utility of this approach.

**Alkylating agents.** Maintenance therapy with alkylating agents has not prolonged survival when compared with no therapy, and this approach is no longer recommended.

**Steroids for maintenance.** Two large, randomized trials have shown that glucocorticoid maintenance prolongs the duration of remission and improves life expectancy, although side effects are a concern, particularly with long-term use. The Southwest Oncology Group (SWOG) study used prednisone (50 mg) every other day, whereas the maintenance regimen in the National Cancer Institute of Canada (NCIC) trial included dexamethasone (40 mg) daily for 4 days every 4 weeks. More recent data suggest that the use of lenalidomide with predniosone may be superior to lenalidomide alone in this context.

**Relapsed, and relapsed and refractory disease**

The majority of patients progress after initial relapse, which usually lasts between 18 months and 5 years. Rapid progress is being made in the management of relapsed disease and many new drugs are being introduced in a succession of promising clinical trials, although the entity of relapsed and refractory disease remains a major challenge.

**Conventional chemotherapy.** Alkylating agents, alone or in combination, have been effective in approximately one-third of patients with VAD-refractory disease. Patients relapsing after treatment with novel agents often have responded to alkylating agent therapy, especially in combination with novel agents. Patients presenting with high LDH levels and soft tissue plasmacytoma may respond to combination chemotherapy with cyclophosphamide, etoposide, cisplatin, and dexamethasone (DCEP) with or without doxorubicin, bortezomib, or thalidomide (VDT-PACE). Although this regimen is active, prolonged use is limited by side effects, and the use of novel therapy as part of these regimens appears important in improving efficacy.

**High-dose chemotherapy.** HDM and stem cell rescue should be offered to patients who have deferred the transplant initially. A randomized trial performed in the pre–novel therapy era on early vs late transplantation has shown that an equivalent survival benefit is conferred on patients undergoing salvage, compared with early transplantation, with ongoing studies further evaluating the optimal timing of SCT in the current era of new treatments.

**Novel agents**

**Thalidomide.** Thalidomide has a long-established role in therapy for relapsed and refractory multiple myeloma, with 30% of patients achieving at least a 50% reduction in paraprotein levels. Remissions obtained in responding patients are usually durable. In a large cohort of patients with multiple myeloma receiving thalidomide, 2-year event-free survival rates of about 25% have been observed. Initially, thalidomide was employed in a dose-escalating schedule, starting at 200 mg and achieving a maximal dose of 800 mg. Recently, lower doses have been employed in combination with steroids as well as with other agents and have proved more effective and better tolerated (Table 4).

**Lenalidomide.** Lenalidomide has greater potency than thalidomide in preclinical studies. In clinical trials it has greater efficacy and is better tolerated, with less neurotoxicity, somnolence, and constipation.

Two large, multicenter, phase III trials have been performed of lenalidomide (given at a dose of 25 mg daily for 3 weeks, with 1 week off) combined with dexamethasone compared with dexamethasone and placebo in patients with relapsed multiple myeloma. In the US study, there was
significant improvement in the response rate (PR, 59% vs 21%, respectively) and time to disease progression (11.1 vs 4.7 months, respectively) in the cohort receiving the lenalidomide combination; the results of the second study, from Europe, were almost identical. Similar responses were seen in patients relapsing after prior bortezomib or thalidomide exposure. Prophylaxis against DVT and monitoring for myelosuppression are recommended based on the side effects seen, but lenalidomide is generally well tolerated.

**Proteasome inhibitors.** A large, multi-institution, phase II trial of the proteasome inhibitor bortezomib (given IV at a dose of 1.3 mg/m$^2$ on days 1, 4, 8, and 11 every 21 days) demonstrated remarkable activity of bortezomib in a heavily treated population of patients with relapsed and refractory multiple myeloma, including patients relapsing after transplantation or not responding to thalidomide, with durable responses noted in about 35% (with 10% CR). Side effects related to the drug were predominantly gastrointestinal in nature, with neuropathy, fatigue, and reversible cytopenias also noted. Toxicities were generally manageable with supportive care and dose reduction. Patients who did not respond to bortezomib monotherapy (those with progressive disease after 2 cycles or stable disease after the first 4 cycles) were permitted to receive combination bortezomib and dexamethasone. Combination therapy induced additional responses in 18% of patients.

The large, randomized, phase III APEX trial of bortezomib monotherapy compared with high-dose dexamethasone enrolled 669 patients with relapsed multiple myeloma. This trial showed significant improvement in the median time to disease progression (6.5 vs 3.6 months, respectively; $P < .0001$) and median overall survival (29.8 vs 23.7 months, respectively; $P = .027$). The rate of response to bortezomib as a single agent was impressive at 43%. The most commonly reported adverse events for bortezomib were neuropathy, gastrointestinal events, fatigue, pyrexia, and thrombocytopenia; for high-dose dexamethasone, they included fatigue, insomnia, and anemia. Neuropathy was the most important issue with bortezomib, but it proved generally manageable with dose reduction and schedule change. DVT was very rare, and efficacy in patients with significant renal dysfunction was noted. Finally, encouraging responses were noted in patients with adverse cytogenetics as well as in patients with advanced bone disease.

Bortezomib has synergistic activity when combined with pegylated liposomal doxorubicin, thalidomide, melphalan, and lenalidomide, with impressive disease control shown in refractory myeloma. In a randomized, phase III, multicenter, international study in patients with relapsed/refractory myeloma, the combination of bortezomib (1.3 mg/m$^2$ on days 1, 4, 8, and 11) and pegylated liposomal doxorubicin (30 mg/m$^2$ on day 4) was reported to be superior to bortezomib alone in terms of both overall response (50% vs 42%, respectively; $P = .05$) and time to disease progression (9.3 months vs 6.5 months, respectively; $P < .0001$). When bortezomib (at a dose of 1 mg/m$^2$ or 1.3 mg/m$^2$) was administered with thalidomide (in doses ranging from 50 to 200 mg starting at cycle 2), 86% of patients with relapsed or refractory disease achieved a complete or partial response and randomized data have recently demonstrated the superiority of this approach to thalidomide/dexamethasone in relapsed multiple myeloma. A phase II study combining bortezomib with lenalidomide and dexamethasone (RVD) has also shown promising activity with relatively limited toxicity.

**Carfilzomib.** Carfilzomib is an irreversible proteasome inhibitor which selectively targets the chemotrypsine-like activity of the proteasome. Its activity as a single agent has been demonstrated in relapsed/refractory multiple myeloma patients who are bortezomib-naive or refractory. An ORR of about 50% was achieved in a cohort of 129 bortezomib-naive patients, while the ORR was approximately 20% in bortezomib-treated patients. Side effects are manageable and include hematologic toxicity, fatigue, dyspnea, and gastrointestinal problems. Interestingly, the rate of neuropathy seen has been low. However, use of carfilzomib is associated with a risk of cardiologic events (congestive heart failure) and patients should be carefully monitored.

Results of the phase III randomized ASPIRE trial firmly established that a three-drug combination is superior to a two-drug combination. A regimen comprising carfilzomib, lenalidomide, and dexamethasone was superior to one with lenalidomide and dexamethasone in terms of ORR (87% vs 67%), CR rate (32% vs 9.3%), and median progression-free survival (26.3 mos vs 17.6 mos). In the interim analysis there was no difference in survival, but the trend favored triplet therapy.

**Pomalidomide.** Pomalidomide is a third-generation IMiD that has recently been FDA-approved for relapsed or refractory multiple myeloma. Indeed, when used in combination with dexamethasone, the ORR ranges from 20% to 35% in heavily pretreated patients who are notably lenalidomide-refractory and/or bortezomib-refractory. The multicentric randomized MM-003 trial has demonstrated a significant advantage in both progression-free survival (median, 4 months) and
overall survival (median, 12.7 months) by using pomalidomide along with dexamethasone compared to high-dose dexamethasone alone in relapsed/refractory multiple myeloma. Moreover, the advantage in the survival was seen in the lenalidomide (progression-free survival and overall survival improvements) and bortezomib- and lenalidomide-refractory (progression-free survival improvement) subgroups. In those subgroups, an ORR of about 30% was achieved. The drug is well tolerated and the most common side effects include myelosupression, infections, fatigue, or bone pain. Treatment with pomalidomide requires a thromboembolic prophylaxis similar to that used with the other IMiDs. Pomalidomide is a promising agent and its use in combination therapy along with proteasome inhibitor or alkylator agents is currently being evaluated in relapsed and/or refractory multiple myeloma. Moreover, based on cytogenetics or GEP findings, high-risk patients might benefit from its use.

**Bendamustine.** Bendamustine, although not FDA-approved for myeloma, can offer a good response for patients with relapsed and refractory multiple myeloma. An ORR of 48% was seen in a phase I/II trial combining bendamustine with bortezomib in relapsed/refractory multiple myeloma. Another trial in combination with lenalidomide reported an ORR of 52%, with 24% achieving VGPR. Its association with prednisone has been compared in the late 1990s to melphalan–prednisone in the newly diagnosed multiple myeloma. The ORR was 75%, with a 32% CR rate, and showed a 4-month benefit in the time to treatment failure. Nausea/vomiting and hematologic (leukopenia, thrombocytopenia) side effects are mainly described.

### Promising novel agents

**Proteasome inhibitors.** Treatment with ixazomib as a single agent yields an approximately 15% ORR in bortezomib nonrefractory patients. It achieves a 34% ORR in combination with dexamethasone. A phase I/II trial has evaluated a totally oral induction regimen (ixazomib–lenalidomide and dexamethasone). The ORR in this trial was 94%, with 76% achieving more than VGPR. Rare peripheral neuropathy has been described; notably, the side effects included rash. Its use in maintenance therapy along with lenalidomide is currently being evaluated. The interim results of TOURMALINE-2, a randomized, double-blind, placebo-controlled trial, showed that a combination of ixazomib, lenalidomide, and dexamethasone is superior to a two-drug regimen of lenalidomide and dexamethasone.

Oprozomib is an oral available analog of carfilzomib. A phase I/II study including multiple myeloma has shown a good safety profile. Adverse events were mostly cytopenia and gastrointestinal symptoms.

**Monoclonal antibodies.** The activity of monoclonal antibodies is related to different pathways. Besides the direct cytotoxicity from inducing apoptosis, the antigen-dependent cellular cytotoxicity and complement-dependent cytotoxicity are involved in their effect. Elotuzumab is a humanized monoclonal antibody (IgG1) directed against the SLAMF7 glycoprotein expressed on myeloma cells and involved in the adhesion to bone marrow stroma cells. Phase I and II studies have shown a synergistic activity of elotuzumab in combination with lenalidomide, with an encouraging ORR in relapsed multiple myeloma of about 80% and prolonged progression-free survival (up to 33 months). Toxicities are manageable and include neutropenia, thrombocytopenia, fatigue, gastrointestinal issues, and infusion-related events. Current phase III trials are comparing the outcome of the association of lenalidomide–dexamethasone with or without elotuzumab in relapse or in newly diagnosed myeloma. Its use in association with VRD is also under investigation. Daratumumab is an anti-CD38 monoclonal antibody that has so far showed impressive results in monotherapy or in combination with lenalidomide and dexamethasone. Investigators of a phase I/II trial have reported an ORR of 100% and a rate of VGPR or better than 50% on 6 patients with relapsed or refractory multiple myeloma treated with lenalidomide, dexamethasone, and daratumumab. Neutropenia and infusion reaction were the main side effects. Another anti-CD38 antibody, SAR 650984, has also demonstrated its safety and efficacy as monotherapy in highly pretreated patients, achieving an ORR of 26.5%.

Other monoclonal antibodies include anti-CD138 (BT032), anti-CD56, or anti-CD40. As with the other monoclonal antibodies, BT 062 has showed synergistic activity along with lenalidomide, achieving an ORR of 72% in relapsed or refractory patients.

**Histone deacetylase (HDAC) inhibitors.** Panobinostat is the first HDAC inhibitor to receive accelerated approval for treatment of patients with relapsed myeloma in whom at least two prior regimens have failed. Approval was based on the results of PANORAMA1, an international, randomized, placebo-controlled, double-blind phase III trial. Patients receiving panobinostat, bortezomib, and dexamethasone had a higher CR or near-CR (28% vs 16%) and a longer...
progression-free survival (median progression-free survival, 12 mos vs 8 mos) with no difference in overall survival at the time of the interim analysis. Patients in the phase II PANORAMA2 study demonstrated a 35% ORR, a 5.4-month median progression-free survival, and a 17.5-month median overall survival in a bortezomib-refractory population. Its use with lenalidomide is also being evaluated. The adverse events encountered were thrombocytopenia and frequent gastrointestinal side effects, including diarrhea and fatigue.

Vorinostat is a HDAC inhibitor. Although the first results seemed encouraging in terms of its combination with proteasome inhibitors, results of a phase III trial investigating the triplet bortezomib–vorinostat–dexamethasone in patients with relapsed multiple myeloma have only shown a 0.8-month difference in progression-free survival in comparison to results with bortezomib-dexamethasone. The ORR was better (56.2% vs 40.6%). These results were overcome by the adverse events encountered (thrombocytopenia, frequent gastrointestinal side effects, and fatigue).

ACY-1215 is a selective HDAC6 inhibitor that demonstrated an activity when administered in combination therapy, similar to that observed with the other deacetylase inhibitors. The ORRs reported were 25% in association with bortezomib in 20 heavily pretreated patients, and 69% in association with lenalidomide in 12 patients. Gastrointestinal side effects were rare.

**Spindle kinase protein inhibitor.** ARRY 520 has shown activity as monotherapy and in combination with dexamethasone. The ORR reported was about 15%. Half of the patients experienced grades 3 and 4 myelosuppression. Thus, the use of ARRY 520 requires growth factor support. Its association with proteasome inhibitors is currently being evaluated.

Other small molecules under study include the orally bioavailable agent, perifosine, which targets AKT, JNK, and NFKB. Combinations with bortezomib and lenalidomide have shown encouraging results, but unfortunately a phase III trial of perifosine combined with bortezomib and dexamethasone was discontinued when a significant difference in progression-free survival, the primary endpoint, was not achieved at interim analysis.

**Allogeneic stem cell transplantation.** For younger patients with resistant relapsed or poor-prognosis disease (eg, with deletion of chromosome 13), allogeneic transplantation may be an important option. The role of allogeneic transplant in myeloma should still be considered investigational. High-dose myeloablative therapy with allogeneic stem cell rescue has been abandoned in light of high transplant-related mortality. A nonmyeloablative regimen is ineffective in tumor cytoreduction and, consequently, is related to a high relapse rate. Thus, uniquely in multiple myeloma, high-dose melphalan and stem cell transplant is followed by a nonmyeloablative regimen and allogeneic stem cell transplantation. Two large, randomized trials from France and Italy that compared tandem autologous transplantation with autologous transplantation followed by allogeneic transplantation from matched sibling donors had different outcomes. French investigators noted no improvement in progression-free survival or overall survival when inclusion criteria were restricted to a high-risk group, whereas Italian investigators noted better event-free survival and overall survival when no such restriction for patient entry to the study was in place. In addition, chronic graft-vs-host disease inflicts considerable morbidity, in excess of 50% of patients post-allograft. Currently, use of allogeneic stem cell transplantation is only recommended in the context of a clinical trial.

**Supportive therapy**

Various supportive therapies may be beneficial in patients with multiple myeloma (Table 6).

**Table 6: Supportive therapies for multiple myeloma**

**Chronic anemia.** The use of erythropoietic-stimulating agents (ESAs) in myeloma should generally be restricted to patients who are anemic due to concomitant chemotherapy or moderate-to-severe renal failure. The combined use of ESAs and immunomodulatory agents is associated with an increased incidence of venous thromboembolism, but this is not seen with bortezomib. For additional information about the use of ESAs in patients with cancer, visit the [FDA information page on ESAs](http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm197072.htm).

**Infection.** Serious infection with encapsulated organisms is encountered by patients with myeloma due to their inability to mount successful antibody production (and lack of opsonization). Prompt institution of antibiotics is therefore recommended in the face of systemic infection. Antibiotic prophylaxis is also recommended whenever high-dose glucocorticoids are used for treatment. Patients with recurrent serious infections may benefit from monthly intravenous gamma globulin.
Shingles is not uncommon in myeloma patients, and prophylaxis following transplantation and during bortezomib therapy is advised with appropriate antiviral therapy.

**Bone pain or imminent fracture.** Therapy with bisphosphonates, such as pamidronate or zoledronic acid, has been shown to reduce skeletal-related events and improve quality of life for patients with multiple myeloma. Bisphosphonates reduce skeletal-related events including bone pain, hypercalcemia, lytic bone disease, and compression fractures. There is reduction in the incidence of skeletal-related events within the first year of starting therapy, even in patients presenting with no lytic bone disease. A recent large randomized trial from the MRC in the UK of newly diagnosed symptomatic myeloma patients has shown continuous therapy with zoledronic acid until progression improves progression-free survival and overall survival. The risk of osteonecrosis of the jaw was 3% to 5% in this study, and there was no increased incidence of renal impairment. Zoledronic acid, the more potent amino-bisphosphonate, has efficacy and safety comparable to pamidronate in preventing skeletal lesions. The ease of administration of a 4-mg dose, which reduces the infusion time to 15 to 30 minutes compared with 2 hours for pamidronate, has led to FDA approval of zoledronic acid for prevention of bone-related complications in myeloma. Caution should be exercised with long-term use of bisphosphonates, since renal impairment and osteonecrosis of the jaw bones have been reported, as previously mentioned. Percutaneous vertebroplasty provides pain relief that is not only rapid but sustained, and it also strengthens the vertebral bodies. Kyphoplasty is a safer procedure that involves insertion of a balloon followed by injection of polymethyl methacrylate, the principal component of bone cement, into the balloon. It is performed with the patient under local anesthesia. Transient worsening of pain and fever that may occur is responsive to nonsteroidal anti-inflammatory agents.

**Smoldering Myeloma**

Smoldering, or asymptomatic, myeloma is characterized by the presence of monoclonal Ig > 3 g/dL and/or bone marrow plasmacytosis in excess of 10%. The diagnosis is often made by a chance finding of an elevated serum protein level during a screening examination.

**Laboratory features**

Features of low tumor mass are usually present, without renal disease, hypercalcemia, or lytic bone lesions (Table 2). Marrow plasma cytosis occurs in less than 30% of patients, and anemia, if present, is mild (hemoglobin value > 10.5 g/dL).

**Treatment**

Systemic therapy should be withheld until the patient becomes symptomatic, although studies are now evaluating various novel agents in this setting. The role of bisphosphonates and lenalidomide has been evaluated, and a series of studies have suggested benefit from reducing the incidence of bone complications and increasing the time to progression with bisphosphonate use. The use of lenalidomide and dexamethasone in populations at particularly high risk has been associated with an overall survival benefit, and trials in this area are ongoing. An MRI finding of multifocal plasmacytomas or FDG-PET/CT findings of multifocal osseous lesions would be considered to be evidence of end-organ damage, and should warrant initiation of additional therapy.

**Prognostic factors.** Smoldering myeloma generally progresses to multiple myeloma at the rate of 10% per year for the first 5 years, 3% per year for the next 5 years, and then 1% for the last 10 years. The initial concentration of serum monoclonal protein > 3 g/dL, bone marrow plasmacytosis > 10%, and an abnormal serum free light chain ratio are significant predictors of progression to symptomatic myeloma.

**Other Plasma Cell Dyscrasias**

Other plasma cell dyscrasias include MGUS, solitary plasmacytoma of bone (SPB), solitary extramedullary plasmacytoma, Waldenström’s macroglobulinemia, amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, and heavy-chain diseases.

**Monoclonal Gammopathy of Unknown Significance**

MGUS occurs in 1% of normal individuals > 40 years old, and its frequency rises progressively with age. Recent studies indicate that the diagnosis of symptomatic multiple myeloma is always preceded by monoclonal gammopathy for 2 or more years.
Laboratory features

Common laboratory features of MGUS are listed in Table 2.

Treatment

Approximately 25% of patients with this disorder develop multiple myeloma, macroglobulinemia, or non-Hodgkin lymphoma over a period of 20 years post-diagnosis. The initial concentration of serum monoclonal protein > 1.5 g/dL, non-IgG-type paraprotein, and abnormal serum free light-chain ratio are significant predictors of disease progression at 20 years. The long period of stability supports annual monitoring with serum electrophoresis and blood counts and suggests that chemotherapy may be withheld until there is evidence of progression to myeloma.

Solitary Plasmacytoma of Bone

Approximately 3% of patients with myeloma have solitary plasmacytoma of bone (SPB).

Laboratory features

All patients have either no myeloma protein or very low levels in serum or urine (Table 2). MRI may reveal abnormalities not detected by bone survey and may upstage patients to multiple myeloma. Persistence of monoclonal protein for more than 1 year after irradiation predicts early disease progression to multiple myeloma.

Treatment

Management of SPB consists of radiation therapy (at least 45 Gy). Multiple myeloma becomes evident in most patients over time, so only 20% of patients remain free of disease for more than 10 years. The median time to disease progression is approximately 2 to 3 years.

Solitary Extramedullary Plasmacytoma

In contrast to SPB, solitary extramedullary plasmacytoma is often truly localized and can be cured in up to 50% of patients with localized radiation therapy (45–50 Gy) and/or resection. Careful observation after treatment is nonetheless warranted.

Waldenström’s Macroglobulinemia

This uncommon disease is characterized by lymphoplasmacytic bone marrow and tissue infiltrate in addition to elevated IgM production. The mutation pattern analysis suggests that final transformation occurs in the postgerminal center IgM memory B cell. Corresponding with variation in cell morphology, there is variation in the immunophenotype. Mature plasma cells exhibit CD38 antigen; however, lymphoid cells are typically positive for CD19, CD20, and CD22. Waldenström’s macroglobulinemia usually affects people in the fifth to seventh decades of life and can cause symptoms due to tumor infiltration (marrow, lymph nodes, and/or spleen), circulating IgM (hyperviscosity, cryoglobulinemia, and/or cold agglutinin hemolytic anemia), and tissue deposition of IgM (neuropathy, glomerulonephritis, and/or amyloidosis). Neuropathy may be due to the IgM antibody reacting with myelin-associated glycoprotein.

Hyperviscosity syndrome

With hyperviscosity syndrome, patients may have visual symptoms, dizziness, cardiopulmonary symptoms, decreased consciousness, and a bleeding diathesis. Therapy for hyperviscosity consists of plasmapheresis followed by chemotherapy to control the malignant proliferation. Patients with poor performance status and elderly patients who are unable to tolerate chemotherapy may be maintained with periodic plasmapheresis.

Treatment

Alkylating agents used in combination with steroids or purine analogs remain the mainstay of therapy. Alkylating agents alone or in combination with steroids effect a 50% reduction in paraprotein in about half of patients, and the median survival time is around 5 years. The purine analogs fludarabine (Fludara) and cladribine (Leustatin) elicit a more rapid response than other agents, with a response rate of more than 75% observed in a small series of patients. Preliminary results of a large, American multi-institution evaluation of fludarabine reported partial responses in only 33% of patients. Purine analog therapy may result in significant myelosuppression in later cycles of therapy and prolonged immunosuppression with increased opportunistic infections. Purine analogs are effective
salvage options in patients refractory to or relapsing following alkylator therapy. Patients refractory to one purine analog are rarely salvaged by a different purine analog. Patients with resistant relapse are less likely to benefit from purine analogs (response rate, 18%) and should be considered for more intensive intervention, including high-dose therapy.

**Other treatment options**

Rituximab (Rituxan), an anti-CD20 monoclonal antibody, is effective in Waldenström’s macroglobulinemia, because the CD20 antigen is usually present on the lymphoid cell component of macroglobulinemia. Preliminary results indicate that about 30% of previously treated patients (refractory or relapsing while off therapy) may benefit from rituximab.

Striking activity of thalidomide in multiple myeloma has prompted its use in Waldenström’s macroglobulinemia. In a series of 20 patients receiving thalidomide, 25% achieved a 50% reduction in paraprotein. Higher doses of thalidomide were not well tolerated in an elderly cohort of patients. Interestingly, preliminary results of bortezomib-based therapy in relapsed Waldenström’s macroglobulinemia have been very promising. In contrast, lenalidomide has proved less useful, primarily because of myelosuppression.

High-dose therapy with autologous bone marrow or blood stem cell rescue has been effective in achieving 50% reduction in paraprotein in almost all patients in small pilot trials.

**Amyloidosis**

Amyloidosis occurs in 10% of patients with multiple myeloma. This infiltrative process results from organ deposition of amyloid fibrils, which consist of the NH2 terminal amino acid residues of the variable portion of the light-chain Ig molecule. The abnormal protein is produced by clonal plasma cells.

**Clinical features**

These include the nephrotic syndrome, cardiomyopathy, hepatomegaly, neuropathy, macroglossia, carpal tunnel syndrome, and periorbital purpura.

**Laboratory features**

Serum and urine immunofixation studies show a monoclonal immunoglobulin in approximately 80% of patients. Measurement of serum free light chain may provide a marker to evaluate response to therapy. The light chain is more frequently of the λ type than the κ type. Diagnosis can be made by the presence of apple-green birefringence on polarized light examination of subcutaneous fat aspirates stained with Congo red. Elevated serum B-type natriuretic peptide levels may indicate cardiac involvement, which, in the majority of patients, may be confirmed with echocardiography.

**Treatment of primary amyloidosis (AL; monoclonal protein-associated)**

Survival of patients with amyloidosis is variable. Patients with congestive heart failure have a median survival of only 4 months. Oral MP extends the median survival to 17 months, as compared with 13 months in untreated patients. Complete hematologic response is rare; similarly, reversal of organ damage is uncommon.

In a large cohort of patients receiving high-dose melphalan with stem cell support, a complete hematologic response was observed in 47% of patients with at least 1 year of follow-up. However, the transplant-related mortality is high with high-dose therapy (14% to 37%). Complete hematologic response was associated with improved clinical response (improved organ function) and survival. Complete hematologic response in the absence of cardiac involvement predicted excellent outcome (1-year survival, 91%). Phase I and II studies have also shown encouraging results with bortezomib as well as lenalidomide, both in newly diagnosed and more advanced disease. Most recently, the combination of cyclophosphamide, bortezomib, and dexamethasone has emerged as an important new option for patients.

Patients with the overlap syndrome of myeloma and AL amyloidosis should be treated aggressively for myeloma; response can be seen in terms of both myeloma and resolution of amyloid symptoms.

**POEMS Syndrome**

**Clinical features and course**

The POEMS syndrome is a rare plasma cell dyscrasia that presents with peripheral, usually sensorimotor, neuropathy; monoclonal gammopathy (IgA λ being more common); sclerotic bone lesions, noted in nearly all patients; and organomegaly, endocrinopathy, and skin changes.
Other features include hyperpigmentation, hypertrichosis, thickened skin, papilledema, lymphadenopathy, peripheral edema, hepatomegaly, splenomegaly, and hypothyroidism. Diabetes mellitus is not part of this syndrome.

Compared with patients with symptomatic myeloma, individuals with POEMS syndrome are younger (median age, 51 years) and live longer (median, 8 years). The clinical course is commonly characterized by progressive neuropathy.

**Treatment**

Plasmapheresis does not appear to be of benefit in POEMS syndrome, and patients are often treated similarly to those with myeloma. Patients presenting with isolated sclerotic lesions may have substantial resolution of neuropathic symptoms after local therapy for plasmacytoma with surgery and/or radiotherapy. Autologous stem cell transplantation has been pursued in selected patients and has been associated with prolonged progression-free survival.

**Heavy-Chain Diseases**

Heavy-chain diseases are rare plasma cell dyscrasias characterized by the production of heavy-chain Ig molecules that lack light chains (IgG, IgA, IgM).

**α Heavy-chain disease**

This condition results from lymphocyte and plasma cell infiltration of the mesenteric nodes and small bowel and has features of malabsorption, such as diarrhea, weight loss, abdominal pain, edema, and nail clubbing. The heavy-chain molecule may be detected in serum, jejunal secretions, and urine. There is an association with infection with *Campylobacter jejuni* and α heavy-chain disease. Large proportions of patients can benefit from antibiotic therapy directed at this infection.

**γ Heavy-chain disease**

Patients with γ heavy-chain disease may present with fever, weakness, lymphadenopathy, hepatosplenomegaly, and involvement of Waldeyer’s ring. Eosinophilia, leukopenia, and thrombocytopenia are common. Treatment with regimens similar to those used for non-Hodgkin lymphoma may be effective.

**μ Heavy-chain disease**

This condition is seen exclusively in patients with chronic lymphocytic leukemia (CLL). Vacuolated plasma cells are common in the marrow, and many patients have κ light chains in the urine. Therapy is similar to that used for CLL (see the “Chronic Lymphocytic Leukemia and Hairy-Cell Leukemia” chapter).

**Suggested Reading**

**On Multiple Myeloma**


Multiple Myeloma and Other Plasma Cell Dyscrasias
Published on Physicians Practice (http://www.physicianspractice.com)


**On Other Plasma Cell Dyscrasias**


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