PET and MRI are considered to further evaluate bone disease and may be necessary for patients with oligosecretory or nonsecretory disease to define disease and evaluate after therapy. Conventional bone scans are less useful due to the osteolytic nature of myeloma.

About 20% of patients with multiple myeloma do not have detectable serum M protein by standard electrophoresis but have circulating free light chains that may be detectable by serum free light-chain assays. Free light chains may appear in the urine (i.e., Bence Jones protein) and can also be detected in a 24-hour urine collection by urine protein electrophoresis. In rare cases, patients with nonsecretory myeloma have neither detectable serum nor urine M protein. Free light-chain assays are quite sensitive and may provide measurement of clonal protein in patients thought to have nonsecretory disease by other methods. Free light chains have a relatively short half-life (2 to 6 hours) in the circulation compared with weeks for intact immunoglobulin molecules and may therefore be used to obtain a more rapid assessment of disease response for patients on therapy.

Clinical Presentation

The clinical manifestations of multiple myeloma are the direct effects of bone marrow and bone infiltration by malignant plasma cells, the systemic effects of the M protein, and the effects of the concomitant deficiency in humoral immunity that occurs in this disease. The most common symptom in multiple myeloma is bone pain. Bone radiographs typically show pure osteolytic punched-out lesions, often in association with generalized osteopenia and pathologic fractures. Bony lesions can show as expansile masses associated with spinal cord compression. Hypercalcemia caused by extensive bony involvement is common in myeloma and may dominate the clinical picture. Anemia occurs in most patients as a result of marrow infiltration and suppression of hematopoiesis and causes fatigue; granulocytopenia and thrombocytopenia are less common.

Patients with myeloma are susceptible to bacterial infections because of impaired production and increased catabolism of normal immunoglobulins. Gram-negative urinary tract infections are common, as are respiratory tract infections caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae,* and *Klebsiella pneumoniae*.

Renal insufficiency occurs in about 25% of patients with myeloma. The cause of renal failure is often multifactorial; hypercalcemia, hyperuricemia, infection, and amyloid deposition can contribute. However, direct tubular damage from light-chain excretion invariably occurs. Because of their physicochemical properties, M proteins can cause a host of diverse effects, including cryoglobulinemia, hyperviscosity, amyloidosis, and clotting abnormalities resulting from interaction of the M protein with platelets or clotting factors.

Several staging or classification systems exist for myeloma. The International Staging System (ISS) for myeloma identifies three stages with distinct prognoses based on only two variables: β_2-microglobulin and albumin levels (Table 49-6).

TABLE 49-6 INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA

STAGE	CRITERIA	SURVIVAL TIME (mo)
I	B2M <3.5 mg/L Albumin ≥3.5 g/dL	62
II	Not stage I or III	44
III	B2M >5.5 mg/L	29

Greipp PR, San Miguel J, Durie BG, et al: International staging system for multiple myeloma, *J Clin Oncol* 23:3412–3420, 2005.

B2M, β_2-Microglobulin.

Treatment

Most patients with myeloma exhibit symptomatic, advanced-stage disease and require therapy. Patients with stage I disease or asymptomatic myeloma may have an indolent course and do not always require immediate therapy. Disease progression occurs at a rate of 5% to 10% per year, and patients should be monitored for disease progression by serial quantification of the M protein and evaluation for disease-related signs or symptoms. For patients with solitary bone or extramedullary plasmacytomas, particularly in the head and neck region, local radiation therapy can induce long-term remissions and is the treatment of choice. Patients with a solitary plasmacytoma of bone are often found on routine MRI of the spine to have asymptomatic bone disease and are at higher risk for progression to myeloma.

Patients with symptomatic myeloma require systemic therapy and meticulous supportive care. Although myeloma is not a curable malignancy, systemic therapy can prolong survival and dramatically improve quality of life. Options for treatment have expanded in the past decade to include multiple compounds in two broad classes of agents, the immunomodulatory drugs (IMIDs) and proteosome inhibitors. These agents may be used as single agents or in combinations for more intensive therapy. They are typically administered in combination with high doses of dexamethasone, which is a potent antimyeloma therapy. The IMIDS include thalidomide, lenalidomide, and pomalidomide. Proteosome inhibitors include bortezomib and carfilzomib. These agents have largely supplanted traditional chemotherapeutic agents as the cornerstone of initial and secondary therapies because they are efficacious and usually well tolerated. Multiple combination regimens have been devised that also incorporate chemotherapeutic agents in modest doses.

Thalidomide is the first-in-class IMID and was initially used as a sedative in the United Kingdom in the 1960s, but it was found to cause birth defects when used to combat nausea during pregnancy. The antiangiogenic properties of thalidomide subsequently led to its development as an anticancer agent. Although the mechanism of action of the IMIDs is unclear, they are now thought to exert antitumor effects primarily through stimulation of immune effectors. The IMIDs are typically used in combination with dexamethasone, and when used as initial therapy, they have good tolerability and result in high response rates.

Toxicity related to thalidomide includes peripheral neuropathy, constipation, somnolence, and rash. Later-generation IMIDs have a more favorable side effect profile. Myelosuppression is more likely, but neuropathy and constitutional symptoms occur less frequently. The second-generation IMID lenalidomide is more commonly used in North America due its favorable tolerability. A troublesome and unique side effect of the IMID-steroid combination programs is development of deep vein