thrombosis in up to 25% of patients, and some form of preventative therapy is typically prescribed.

Bortezomib is the first-in-class proteosome inhibitor and is a favored therapy for patients with adverse cytogenetic risk factors. Bortezomib is typically administered subcutaneously and may cause thrombocytopenia, asthenia, and neuropathy.

Most patients respond to initial therapy with a reduction in bone pain, hypercalcemia, and anemia in association with a decline in the M protein level. The selection of initial therapy depends on stage, cytogenetic risk, and candidacy for high-dose chemotherapy and autologous stem cell transplantation. The use of high-dose chemotherapy with alkylating agents followed by autologous peripheral stem cell infusion during first or second remission has improved survival and quality of life compared with standard doses of chemotherapy. Although this approach is not curative, it does represent an important treatment option for some patients and has an acceptable toxicity profile, even in older patients. The relative value of autologous stem cell transplantation compared with ongoing therapy with the newer agents is unknown and is an area of active clinical investigation. Allogenic stem cell or bone marrow transplantation may be associated with durable remission in selected patients, but it carries a much higher near-term risk of morbidity and mortality. Patients who experience relapse after standard therapy or transplantation may be treated with alternate chemotherapy regimens or with novel combination therapies, including newer agents and chemotherapy drugs.

Supportive care directed toward anticipated complications of myeloma is an important aspect of the management of this disease. Bone resorption can be reduced with regular injections of the diphosphonates zoledronic acid or pamidronate, reducing pain and pathologic fractures. Bony lesions, particularly those involving weight-bearing bones, may require palliative irradiation for controlling pain and preventing pathologic fractures. Vertebral bony lesions may lead to spinal cord compression, with increasing back pain and neurologic symptoms. Symptoms suggesting cord compression require prompt evaluation with spinal MRI and, if necessary, local irradiation of involved areas.

Avoidance of nephrotoxins, including intravenous dyes, is important to prevent renal failure. All patients should receive pneumococcal and *H. influenzae* vaccines, and intravenous gamma globulin may be useful in preventing recurrent infections in patients with profound hypogammaglobulinemia. Use of erythropoietin may alleviate anemia and decrease the need for blood transfusions.

Prognosis

Multiple myeloma is considered incurable, but the overall survival of these patients has improved considerably with the widespread use of autologous stem cell transplantation and development of newer agents. For example, median survival reported by the Mayo Clinic has increased from 29 to 44 months.

The prognosis depends on the stage of disease and cytogenetic profile. Patients with an adverse karyotype, including t(14;16) and 17p deletion, have a less favorable prognosis and are considered for more intensive therapies or clinical investigation. Adverse factors also include advanced stage, impaired renal function, elevated LDH levels, abnormal bone marrow cytogenetics, depressed serum albumin levels, and elevated β_2-microglobulin levels.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia is a malignancy of plasmacytoid lymphocytes that secrete large quantities of IgM. It is a chronic disorder affecting elderly patients (median age of 64 years) that shares features of the low-grade lymphomas and myeloma. Unlike myeloma, Waldenström macroglobulinemia is associated with lymphadenopathy and hepatosplenomegaly, and although bone marrow involvement invariably occurs, lytic lesions and hypercalcemia are rare.

The major clinical manifestations of Waldenström macroglobulinemia include symptomatic anemia and the hyperviscosity syndrome caused by the physical properties of IgM. In contrast to IgG, IgM remains largely confined to the intravascular space, and as IgM levels rise, plasma viscosity increases. Epistaxis, retinal hemorrhages, dizziness, confusion, and congestive heart failure may occur as a result of the hyperviscosity syndrome. About 10% of IgM proteins have properties of cryoglobulins, and patients show symptoms of cryoglobulinemia or cold agglutinin syndrome demonstrated as acrocyanosis, Raynaud's phenomenon, and vascular symptoms or hemolytic anemia precipitated by exposure to cold. Some patients with Waldenström macroglobulinemia may develop a peripheral neuropathy that may antedate the appearance of the neoplastic process.

The approach to and treatment of Waldenström macroglobulinemia are similar to those of other low-grade B-cell lymphomas. The use of nucleoside analogues such as fludarabine or an alkylating agent, alone or in combination with prednisone, is effective in decreasing adenopathy and splenomegaly and controlling the M spike, but it is not curative. Rituximab has activity against Waldenström macroglobulinemia, as has the proteosome inhibitor bortezomib. The use of rituximab may be complicated by initial worsening of hyperviscosity in patients with high IgM burdens. Plasmapheresis is highly effective in acutely decreasing serum IgM levels and is often needed initially to treat hyperviscosity. Although complete remissions are rare, patients who respond to therapy have median survivals of 4 years, and some patients survive more than a decade.

Rare Plasma Cell Disorders

Heavy-chain disease is a rare lymphoplasmacytoid neoplasm characterized by production of a defective heavy chain of the γ, α, or μ type. The clinical manifestations vary with the type of heavy chain secreted. The γ-type heavy-chain disease is associated with lymphadenopathy, Waldeyer's ring involvement with palatal edema, and constitutional symptoms. The α-type heavy-chain disease, also known as Mediterranean lymphoma, is characterized by lymphoid infiltration of the small intestine with associated diarrhea and malabsorption. The μ-type heavy-chain disease is associated with CLL.

Primary amyloidosis is a systemic illness characterized by deposition of immunoglobulin light chains in organs and tissue, resulting in an array of symptoms caused by organ dysfunction. Congestive heart failure, bleeding diathesis, nephrotic syndrome, and peripheral neuropathy are common complications. Patients with primary amyloidosis may respond to selected treatments