Patients with characteristic clonal CLL cells in the blood to a lesser degree as an isolated abnormality are thought to have monoclonal B-cell lymphocytosis and may be observed.

Clinical Presentation

CLL cells accumulate in bone marrow, peripheral blood, lymph nodes, and spleen, resulting in lymphocytosis, lymphadenopathy, splenomegaly, and ultimately decreased bone marrow function. CLL is also frequently associated with immune dysregulation, exhibited as hypogammaglobulinemia with an increased risk of bacterial infections and autoimmune phenomena such as Coombs-positive hemolytic anemia or immune thrombocytopenia. Some patients exhibit lymphadenopathy, symptoms related to cytopenias, or occasionally, recurrent infections. As the disease progresses, patients develop generalized lymphadenopathy, hepatosplenomegaly, and bone marrow failure. Death often results from infectious complications or bone marrow failure after patients have become refractory to treatment. In about 5% of cases, CLL transforms to a highly malignant diffuse large cell lymphoma, which is usually rapidly fatal. This transformation is commonly referred to as Richter's syndrome.

Treatment

CLL is a low-grade leukemia or lymphoma that is typically characterized by a long natural history with slow progression over years or decades. Median survival is in excess of 6 years. The extent of disease (stage) at onset is the best predictor of survival. In the absence of immune phenomena, anemia and thrombocytopenia are signs of advanced-stage disease associated with poor survival.

Because standard therapy is not curative and CLL may have an asymptomatic phase lasting years, specific treatment is often withheld until signs of disease progression or development of symptoms (e.g., bulky lymphadenopathy, constitutional symptoms such as fevers, cytopenias caused by bone marrow infiltration). The rate of rise of the white blood cell count may also be used to predict development of symptoms and the need for therapy.

When treatment is required, multiple options for therapy are available. The patient's age, medical condition, and cytogenetic abnormalities may influence the choice of therapy. Active chemotherapeutic agents include several alkylating agents (e.g., chlorambucil, cyclophosphamide), the nucleoside analogue fludarabine, or the novel agent bendamustine. The monoclonal anti-CD20 antibody rituximab has activity against CLL, but it is most effectively employed in combination with chemotherapeutic agents.

Most patients respond to therapy with significant reductions in tumor burden. Fludarabine-based therapies are typically associated with a higher rate of complete remissions compared with other therapies, but they may carry higher risks of infections or marrow stem cell injury. Patients with recurrent or refractory disease may respond to a growing list of monoclonal antibodies. Alemtuzumab, a humanized monoclonal antibody to the CD52 molecule, which occurs on most lymphocytes, is efficacious, including in patients with a 17p deletion, a group for whom conventional chemotherapy works poorly. Additional agents include the anti-CD20 antibodies ofatumumab and obinutuzumab, which was shown to improve remission duration in previously untreated patients when administered in combination with chlorambucil (level I evidence).

Patients with poor-risk cytogenetic abnormalities are more likely to demonstrate resistance to standard therapies and have shortened survival. These patients may be candidates for allogeneic transplantation, which appears to exert a therapeutic effect through a strong immune or graft-versus-leukemia phenomenon. Patients who develop autoimmune phenomena require treatment with corticosteroids, and intravenous gamma globulin may be used to reduce the frequency of infections in patients who have developed hypogammaglobulinemia. The development of a rapidly enlarging mediastinal mass, constitutional symptoms, and high serum LDH level suggests transformation of the disease to a diffuse large cell lymphoma (i.e., Richter's syndrome), which is associated with a poor prognosis.

Plasma Cell Disorders

The plasma cell disorders, or dyscrasias, are a group of clonal B-cell diseases that are related to each other by virtue of their production and secretion of monoclonal immunoglobulin (or part of an immunoglobulin molecule), called the *M protein*. The laboratory hallmark of plasma cell dyscrasias is a homogeneous immunoglobulin molecule (whole or part) that can be detected in the serum or urine by protein electrophoresis. Clinically, these disorders may be characterized by the systemic effects of the M protein and by the direct effects of bone and bone marrow infiltration. Primary amyloidosis, for instance, results in tissue injury through deposition of light chains produced by a clonal population of plasma cells in the absence of an observable proliferation of the plasma cell clone. Waldenström's macroglobulinemia is a disorder with features of NHL and plasma cell disorders. It is discussed in this section because of the distinct clinical effects of the IgM paraprotein produced in this disease.

The most common plasma cell dyscrasia is *monoclonal gammopathy of uncertain significance* (MGUS), followed by multiple myeloma and the closely related plasmacytoma, which is a solitary myeloma of bone or extramedullary soft tissue. Less common plasma cell dyscrasias include osteosclerotic myeloma (i.e., *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy, and *s*kin abnormalities [POEMS syndrome]), heavy-chain disease, and primary amyloidosis.

When an M protein found on serum protein electrophoresis is from individuals with no apparent associated disease and in the absence of any other laboratory or clinical evidence of a plasma cell disorder, it is designated as a MGUS. MGUS is defined by low serum levels of M protein (<3 g/dL), no urinary Bence Jones protein, less than 10% clonal bone marrow plasma cells, and absence of anemia, hypercalcemia, renal failure, and lytic bone lesions. MGUS is more common than myeloma and increases in frequency with aging, occurring in 3% of the population older than 50 years. MGUS is considered a premalignant condition, and patients are at increased risk (sevenfold) for overt myeloma or related malignant plasma cell dyscrasias compared with the general population. Nonetheless, progression of MGUS to a frank plasma cell neoplasm occurs only in about 1% of patients per year.