Lecture 9 in hematology by Dr.Alaa Fadhil Alwan

CHRONIC LEUKEMIAS

1.CHRONIC LYMPHOCYTIC LEUKEMIA(CLL)

CLL is typically a leukemia of elderly people and accounts for about 20% of all NHLs. CLL has a clear male predominance and characterized by the monoclonal accumulation of small, mature-appearing lymphoid cells. The typical CLL belongs to the entity of peripheral B-cell neoplasms, whereas about 5% of all CLLs have a T-cell phenotype. With a sensitive cytogenetic analysis, most cases of CLL have chromosome aberrations. Frequent markers are trisomy 12, aberrations of chromosome 13q, usually predict clinical unresponsiveness. Another important risk factor is Expression of ZAP-70, as well as unmutated status of the immunoglobulin heavy chain genes confers a poorer prognosis.

Clinical Features

Most patients present with enlarged lymph nodes. In early stages, the patients are asymptomatic and have a leukocytosis as the only sign of disease. In later stages, anemia, splenomegaly, and hepatomegaly develop. Some patients also have bruising due to thrombocytopenia, and frequent infections due to neutropenia and hypogammaglobulinemia.

Classification

Rai classification	Binet classification
Stage 0 Lymphocytosis 5000–15000/L	Stage A 0, 1, or 2 lymphatic areas enlarged
Stage I Lymphocytosis + Lymphadenopathy	Stage B 3, 4, or 5 areas enlarged Hb >10 g/dL, Platelets > 100000/L
Stage II As 0 + hepato- and/or splenomegaly	
Stage III As 0 + anemia (Hb <11 g/dL)	Stage C Any lymphatic involvement
Stage IV As 0 + thrombocytopenia (platelets <100000/L) .	Hb <10, and/or platelets <100,000

Laboratory Features

CBP show leucocytosis with mainly lymphocytosis which may be as low as 5000 or higher than 200,000/L. In advanced stages, anemia and/or thrombocytopenia are present. Bone marrow aspiration shows infiltration of the bone marrow with CLL cells (at least 25% of the aspirate, but in many cases as high as 90%). Bone marrow biopsy shows a nodular, diffuse, or mixed infiltration. The bone marrow trephine biopsy may not be necessary in all cases of CLL, as a nodular infiltration has been not confirmed as independent prognostic factor.in advanced, cases, the serum immunoglobulins are decreased (hypogammaglobulinemia). About 5% of patients terminally transform into an aggressive NHL (Richter syndrome).

Prognosis

The prognosis of B-CLL depends on clinical and molecular laboratory features. In early stages, the survival is more than 12 yr (Binet A). In contrast, in advanced stages (Binet C, Rai IV) the median survival is less than 2 yr.

Treatment

The conventional treatment of CLL aims at the palliation of symptoms, not at a cure. In the early stages (Rai 0–II or Binet A or B) the disease may be stable for several years; therefore, no treatment is indicated. If the disease progresses rapidly, if B-symptoms develop, or if the disease leads to complications such as frequent infections or an autoimmune hemolytic anemia, treatment with alkylating agents or fludarabine is indicated in later stages. Supportive therapy plays a major role in the management of patients with CLL. Infections need prompt treatment. Patients with hypogammaglobulinemia and frequent infections may benefit from prophylactic antibiotics or the administration of polyvalent immunoglobulins in case of life-threatening infections.

SINGLE-AGENT CHEMOTHERAPY:1.Chlorambucil **2.** fludarabine .

COMBINED CHEMOTHERAPY:fludarabine and cyclophosphamide (FC) is the best choice. Others e.g COP (cyclophosphamide, Oncovin,and prednisone), CHOP.

2.CHRONIC MYELOGENOUS LEUKEMIA

CML occurs predominantly in adults with a median age of approx 50 yr. It has an incidence of 1–2 per 100,000. CML is a clonal stem cell disorder with a classic cytogenetic abnormality, the Philadelphia chromosome (Ph1), which results from a reciprocal translocation between chromosomes 9 and 22 . At the molecular level, this translocation fuses the BCR gene to the ABL gene on chromosome 9, resulting in a chimeric gene BCR-ABL protein. This BCR-ABL species is typically found in Ph1-positive acute lymphoblastic leukemia. Approximately 90% of patients with CML are found to have the Philadelphia chromosome by routine cytogenetics

Clinical Manifestations

There is usually an insidious onset of symptoms and the diagnosis may be made after a routine blood test for unrelated reasons. Symptoms may relate to the hypermetabolic state associated with a large tumor burden, such as fevers and night sweats. Splenomegaly may cause a feeling of upper abdominal fullness or early satiety. Marked hyperleukocytosis (white blood cell [WBC] >100,000/L) can cause neurological symptoms (such as decreased alertness, confusion, or seizures), visual changes, or, in rare cases, painful erection (priapism). On physical examination, splenomegaly is common, and the spleen may be massively enlarged. Less commonly, hepatomegaly.

Laboratory Abnormalities

In patients with chronic phase CML, the WBC count is invariably increased and may be higher than 200,000/L. The platelet count is frequently increased; thrombocytopenia suggests accelerated or blast phase CML. The hemoglobin concentration is usually normal. The peripheral blood smear is consistent with the diagnosis of CML when the differential includes the spectrum of myeloid cells including metamyelocytes, myelocytes, promyelocytes, and occasional blasts. In the bone marrow, the cellularity is typically 90–100% and it demonstrates marked myeloid hyperplasia with a myeloid:erythroid ratio of 20:1 or higher. The number of blast cells in the bone marrow may be increased, but is below 15%. The leukocyte alkaline phosphatase (LAP) test result is characteristically low in CML, in contrast to leukemoid reactions, for which there is an elevated LAP score. As a consequence of the increased cell turnover, the lactate dehydrogenase (LDH) and uric acid are often increased.

Accelerated phase

Blasts 10–19% in the peripheral blood and/or bone marrow
Basophils ≥20% in the peripheral blood
Persistent thrombocytopenia
Increasing spleen size and white blood cell count despite therapy
Cytogenetic evidence of clonal evolution

Blast phase

Blasts ≥20%
Extramedullary blast proliferation
Large aggregates or clusters of blasts in the bone marrow

2.4. Treatment

There are two prinicpal therapeutic options available: medical therapy with imatinib and allogeneic stem cell transplantation (SCT). Imatinib mesylate is the first “targeted therapy” for leukemia. imatinib 400 mg/d was remarkably effective in this patient population that otherwise had a poor prognosis. Normalization of the peripheral blood counts (complete hematological response) was observed in 95% of patients. Most pt achieve a complete hematological and cytogenetic and molecular response.

Other treatment options interferon alfa, Hydroxyurea.

Pt with blast phase treated as acute leukemia .