CLINICAL-LABORATORY DIAGNOSIS AND TREATMENT METHODS OF CHRONIC MYELOID LEUKEMIA

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Chronic myeloid leukemia (CML) is a disease of the hematopoietic system characterized by the clonal alteration of pathological polypotent stem cells, leading to the formation of abnormal myeloid cells. CML is a clonal myeloproliferative process that develops as a result of transformation of early hematopoietic progenitor cells. The Philadelphia chromosome (Ph chromosome, Ph+), which is an acquired reciprocal translocation between chromosomes 9 and 22 (t(9;22)), is considered the hallmark of CML. The formation of the Philadelphia chromosome occurs as a result of the genetic material exchange between chromosomes 9 and 22. As a result of the genetic material translocation from the 9th chromosome to the 22nd chromosome, the BCR-ABL fusion gene is produced. In CML, there is an excessive production of myeloid progenitor cells.

Chronic myeloid leukemia accounts for 5% of all cases of leukemia in the hematoblast stage (8.9% of cases). The standardized annual incidence rate of the disease is estimated to be one case per 100,000 population. It is equally prevalent among males and females, usually affecting individuals between the ages of 30 and 70, with a lower incidence in childhood and old age.

The etiology is unknown.

The clinical presentation of chronic myeloid leukemia is described with various manifestations due to the heterogeneity of symptoms and the aggressive nature of treatment. In most patients, the initial phase of the disease can last for several years. The signs of the disease are usually detected during routine check-ups or through clinical blood analysis for concomitant pathologies. The clinical manifestations are non-specific and consist of several syndromes.

- Intoxication syndrome: progressive weakness that does not correspond to the degree of anemia, loss of appetite, weight loss, sweating, low-grade fever, bone and joint pain, night sweats, and exacerbation of concomitant diseases.

- Proliferation syndrome: left-sided abdominal pain and a feeling of heaviness, enlargement of the liver.

- Anemia syndrome: general weakness, shortness of breath, pale color of the skin and mucous membranes, rapid heartbeat, hypotension, and signs of cardiovascular diseases.

- Thrombotic manifestations: possible thrombosis and thromboembolism of various organs and tissues during thrombocytosis, as well as thrombophlebitis of

peripheral veins, myocardial infarction, and disruption of cerebral blood flow, which serve as reasons for examination and diagnosis.

- Hemorrhagic syndrome: spontaneous bleeding with minimal trauma or petechiae. This syndrome is usually manifested by thrombocytopenia and becomes more pronounced during the acceleration and blast crisis phases.

In 86-88% of cases of chronic myeloid leukemia, the presence of granulocytes, monocytes, erythrocytes, and megakaryocytes with the Philadelphia chromosome in the bone marrow is detected.

The number of cells with the Philadelphia chromosome in the bone marrow reaches 98-100%. The variant of chronic myeloid leukemia without the Philadelphia chromosome is less common, and the average survival rate of patients is shorter. Confirmation of the diagnosis is made when the Philadelphia chromosome (22q-) is detected as a result of the t(9;22) (q34;q11) translocation or when the oncogene BCR-ABL is detected in the peripheral blood or bone marrow.

Chronic myeloid leukemia has three phases, each characterized by a specific set of symptoms (Table 1):

- Chronic phase
- Accelerated phase
- Blast crisis phase

Table 1. Chronic myeloid leukemia stages according to European classification. (Eng. Europe Leukemia Net, ELN) and world health organization

Chronic myeloid leukemia stages	ELN classification	WHO classification
Chronic	Lack of signs of acceleration phase and blast crisis	
Acceleration	15-29% blast cells in peripheral blood and/or bone marrow; the sum of blasts and pyomyositis is ≥30% (<30%); the number of basophiles in the blood is ≥20%; thrombocytopenia <100×10^9/ l, not related to therapy	15-29% blast cells in peripheral blood and/or bone marrow; the number of basophiles in the blood ≥20%; persistent thrombocytopenia <100≥10^9/ l or thrombocytosis >1000≥10^9/l therapy; increased volume of divorce and leukocytes,not related with therapy; cytogenetic signs of clonal evolution
Blast crisis	The presence of ≥30% blast cells in peripheral blood or bone marrow,extramedullary appearance, infiltration of blast cells	The presence of ≥20% blast cells in peripheral blood or bone marrow, extramedullary appearance, blast proliferation, large stoves or clusters of blasts in the bone marrow trufan biopsy

Chronic stage(chronic phase) - the initial phase of chronic myeloid leukemia; diagnosed in the majority of newly diagnosed patients (more than 80%).

Acceleration phase is identified in 8-10% of patients with chronic myeloid leukemia.

Blast crisis is the most aggressive phase. The debut of blast transformation is an unfavorable prognostic sign and is found in only 1-2% of patients with chronic myelogenous leukemia.

The phase of chronic myeloid leukemia is evaluated at the beginning of the disease as well as during the development period.

In most cases, the diagnosis is based on changes in the number of leukocytes and the characteristic changes in the leukocyte formula in peripheral blood (shift of all mature cells to the left, thrombocytosis, description of basophilia and eosinophilia with displacement of granulocytes to the left). Splenomegaly, thrombocytosis, and basophilia are also characteristic of the initial phase of chronic myeloid leukemia.

The diagnostic protocol for patients with chronic myeloid leukemia includes the following medical services:

- Initial general practitioner examination (history taking, consultation);
- Hematologist consultation;
- Complete blood count, including platelet and reticulocyte count;
- Determination of alkaline phosphatase level in the blood;
- Determination of total protein level in the blood;
- Determination of ALT and AST levels in the blood;
- Determination of sodium, potassium, and calcium levels in the blood;
- Determination of creatinine, urea, and uric acid levels in the blood;
- Determination of iron level in the blood without hemoglobin;
- Determination of LDH level in the blood;
- Serological reaction to various infections and viruses;
- Identification of oncogenes in bone marrow cells;
- Cytological examination of bone marrow aspiration;
- Ultrasound examination of the liver, spleen.
- Cytogenetic examination of bone marrow: confirmation of the presence of translocation t (9; 22) (q34; q11) (Ph chromosomes);
- Molecular genetic examination of peripheral blood: determination of the expression and quantity of BCR-ABL p210 chimeric transcript by PCR.

Cytological diagnosis of chronic myeloid leukemia in the chronic phase:

In peripheral blood:

1. Mild normochromic anemia.
2. Leukocytosis 50-1000x109 / l.
3. Increased ratio of band neutrophils.
4. Presence of metamyelocytes, myelocytes, and promyelocytes in the blood.
5. Granulocytes show anisocytosis, nuclear and cytoplasmic vacuolization, nuclear polymorphism, absence of neutrophil granules (hypo granularity and granularity).
6. Occasional presence of blasts.

7. Association of eosinophils and basophils (increase in the number of eosinophils and basophils).

8. Decrease in lymphocytes.

9. In 40% of cases, thrombocytosis up to 600-1000x109 / l.

In bone marrow:

1. Increased cellularity of the bone marrow.
2. Sharp increase in the granulocytic line.
3. Association of eosinophils and basophils.
4. Presence of blasts up to 10%.
5. Increased number of megakaryocytes.
6. Decreased number of erythrocytes.

Cytological diagnosis of terminal stage chronic myeloid leukemia

Peripheral blood:

1. Severe normochromic anemia.
2. Leukocytosis 50-1000x109/l.
3. Decreased segmented neutrophils.
4. Presence of metamyelocytes, myelocytes, and promyelocytes in the blood.
5. More than 15% blast cells in the blood.
6. Eosinophil-basophil association at times.
7. Rapid decrease in platelet count.

Bone marrow examination:

1. Decreased mature granulocytes.
2. Decreased erythroid and megakaryocytic cell lines.
3. Increased blast cells.

Cytological diagnostic features of chronic myeloid leukemia:

1. Normochromic anemia.
2. Leukocytosis 50-1000x109/l.
3. Increased band neutrophils.
4. Presence of metamyelocytes, myelocytes, and promyelocytes in the blood.
5. Possible presence of blast cells in the blood.
6. Decreased segmented neutrophils.
7. Eosinophil-basophil association.
8. Significant increase in platelet count, followed by a decrease in the terminal stage.
9. Positive myeloperoxidase staining in immature cells.

Complete blood count: In chronic myeloid leukemia: hemoglobin - 75 g/l; red blood cells - 2.0x1012/l, hematocrit - 22%, mean corpuscular volume (MCV) - 100 fl, mean corpuscular hemoglobin (MCH) - 31 pg, leukocytes - 78x109/l. Leukocyte differential count: eosinophils - 7%, basophils - 5%, blast cells - 2%, promyelocytes - 9%, myelocytes - 25%, metamyelocytes - 19%, neutrophils - 18%, segmented

neutrophils - 3%, lymphocytes - 2%. Platelets - 45x109/l, reticulocytes - 0.1%, erythrocyte sedimentation rate (ESR) - 65 mm/hour.

Differential diagnosis: The diagnosis of chronic myeloid leukemia is usually not difficult. In some patients, differential diagnosis starts with the primary manifestation of splenomegaly syndrome.

Complications usually occur in the early stages of the disease, before clear leukemic changes in the blood and distinctive signs of organized metaplasia in the organs have developed. The main pathognomonic sign of the disease is the presence of the Philadelphia chromosome [t(9;22)] and the presence of the chimeric BCR/ABL gene (determined by cytogenetic analysis).

Differential diagnosis is carried out with various infections (sepsis, syphilis) and some tumors (Hodgkin lymphoma, solid tumors), as well as with myeloid leukemoid reactions, which can occur with other chronic myeloproliferative diseases. The main diagnostic criteria for chronic myeloid leukemia are:

• The presence of anemia that is not characteristic of a reactive process;

• An increase in the number of basophils and eosinophils in the leukogram;

• Sometimes there is thrombocytosis;

• Information from the bone marrow examination (increase in the number of myelocytic cells and a sharp shift to the left with chronic myeloid leukemia, slight changes in the bone marrow with a leukemic reaction);

• Dynamics of blood tests (the leukemic reaction usually disappears with the elimination of the cause, along with other changes).

Differential diagnosis with acute leukemia should be made during the blast crisis stage.

Cytogenetic and molecular genetic studies play a role in the differential diagnosis with chronic myeloproliferative diseases (idiopathic myelofibrosis, polycythemia).

Treatment: The current first-line treatment for the chronic phase of chronic myeloid leukemia is the selective BCR-ABL tyrosine kinase inhibitor imatinib at a daily dose of 400 mg.

Alternative approaches include:

- Allogeneic hematopoietic stem cell transplantation;

- Combination therapy with IFN-α and hydroxyurea;

- Second-generation drugs such as dasatinib or nilotinib (Table 2). In all cases, a treatment decision should be made with careful consideration and collegial discussion.

Table 2. Drugs used to treat chronic myeloid leukemia

Non-patented name	Frequency	Output form	K-flour dose	Working dose
Anti-growth,immunosuppressivefactors				
Thyroid inhibitors				
Imatinib	0,8	Tablets	400mg	219000mg
Dasatinib	0.1	Tablets	100mg	3000mg

Nilotinib	0.1	Tablets	600mg	18,000mg
Cytostatic				
Hydroxymochevina	0.1	Capsules	1500mg	90 000mg
Cytarabine	0,05	Ampoules	40mg	2400mg
Treatment and prevention of infections				
Anti-viral therapy				
Interferon	0,5	Ampoules	5mln IU R.	1825mln IU

Monitoring of the patient. During treatment with imatinib in the first phase of patient treatment (with general blood analysis control), the patient should visit the doctor once a week, and then once every 1-2 months.

Cytogenetic examination of bone marrow should be performed every 3 months, and then once a year. Patients who have achieved a complete cytogenetic response should undergo peripheral blood cell testing for BCR-ABL transcript using PCR every 3 months.

The goal of treatment is to achieve a complete molecular response, which corresponds to a relative level of BCR-ABL less than 0.1% on an international scale. Patients who have achieved a complete molecular response have a low risk of relapse.

Prognosis. After 5 years of monitoring, the use of imatinib has shown high rates of hematologic remission (98%), major cytogenetic response (92%), complete cytogenetic response (87%), and disease progression-free survival (84%).

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