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Навчальна дисципліна	Основи внутрішньої медицини
Модуль №	1
Змістовний модуль № 4	Основи діагностики, лікування та профілактики хвороб крові та кровотворних органів
Тема заняття	Гострі та хронічні лейкемії
Курс	4
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Харків 2012

KHARKIV NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF INTERNAL MEDICINE N3

METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS

"Acute and chronic leukemias"

Kharkiv 2012

Module 4. “The basic foundations of diagnostics, treatment and prophylaxis of common hematological diseases”.

Practical lesson N 27

“Acute and chronic leukemias”

Topicality

The annual incidence of leukaemia of all types in the population is approximately 13 per 100,000. They are classified as being acute (short natural history) or chronic (long natural history), and of myeloid or lymphoid origin.

More than half of the leukaemias present acutely (acute limphoblastic leukemia - ALL, acute myelogenous leukemia - AML) with the remainder being chronic types (chronic limphocytic leukemia - CLL, cronic myelogenous CML). The type of leukaemia varies with age; acute lymphoblastic leukaemia is mainly seen in childhood and chronic lymphocytic leukaemia is a disease of the elderly. Males are affected more frequently than females, the ratio being about 3:2 in acute leukaemia, 2:1 in chronic lymphocytic leukaemia and 1.3:1 in chronic myeloid leukaemia.

Interesting age-related patterns of disease exist in ALL and AML.The average age of diagnosis for AML is about 65 years, whereas the average age for ALL is 10 years. This is a result of an increasing incidence of AML with age from about 1.8 per 100,000 in childhood to a peak of 17.7 per 100,000 adults 65 years of age and older. ALL occurs in only about 20% of adult acute leukemia. ALL is the most common malignancy of childhood; the peak incidence is in the 2- to 5-year range. In the pediatric population, leukemia is a common disease, accounting for almost one-third of all childhood malignancies. ALL accounts for 75% to 80% of all cases of childhood leukemia, whereas AML accounts for no more than 20%. Males generally are affected more often than females in all but the infant age group, and its incidence is higher in Caucasians than among other racial groups. The 5-year **event-free survival** rate for ALL is nearly 80% in children and

approximately 40% for adults. For patients with AML younger than 20 years of age, the 5-year survival is 50%. Patients with AML older than age 60 generally have a poorer prognosis of less than 20%.

Educational goals:

- To give definition of acute and chronic leukemias;
- To become familiar with etiology and pathogenesis of different types of acute and chronic leukemia;
- To become acquainted with modern classifications of acute and chronic leukemias;
- To learn methods of investigations of hematological malignancies with special emphasis on indications and contraindications to them;
- To learn how to interpret data of laboratory and instrumental investigations;
- To study how to manage leukemias.

What student should know?

- The basic etiologic factors and pathogenetic mechanisms of leukemia development;
- The basic clinical syndroms of acute and chronic leukemias;
- The chief complants and physical finding in acute and chronic leukemias;
- The methods of physical examination of patients with acute and chronic leukemias;
- The diagnostic value of clinical blood analysis and myelogram in acute and chronic leukemias;
- The diagnostic meaning of sternal puncture, indications and contraindications for this procedure;
- The diagnostic meaning of trepanobiopsy of the iliac bone, indications and contraindications for this procedure;

- The list of instrumental investigations, which allow to identify splenomegaly, hepatomegaly, enlargment of intrisic lymph nodes, leukemic infiltration of different organs;
- The complications of acute and chronic leukemias;
- The particularities of management of patients with leukemias;
- The particularities of leukemias treatment (curative regimen, chemotherapy, supportive care, radiotherapy, bone marrow transplantation);
- The prophylaxis of the leukemias.

What student should know how to do?

- the identification of mean clinical syndromes in acute and chronic leukemias;
- the development of treatment plan of patients with acute and chronic leukemias;
- the interpretation of laboratory findings in case of leukemia;
- the clarification of differential diagnosis;
- the drugs prescription to patients with leukemia;
- the evaluation of prognosis of acute and chronic leukemias

Practical skills:

- Inspection of skin, its derivatives and visible mucous membranes;
- Palpation of peripheral lymph nodes;
- Inspection of abdomen;
- Superficial palpation of abdomen;
- Deep sliding palpation of abdomen (by Obraztsov-Strazhesko method);
- Percussion of liver and spleen.

LEUKAEMIAS

Leucoses (leukaemias) – malignant tumours of a hemopoietic tissue with primary localisation in the bone marrow and with the subsequent dissimination in peripheral blood, spleen, lymph nodes, other organs and tissues.

AetiologyThe cause of the leukaemia is unknown in the majority of patients. Several factors, however, are associated with the development of leukaemia and these are listed below.**Ionising radiation**A significant increase in myeloid leukaemia followed the atomic bombing of Japanese cities. An increase in leukaemia was observed after the use of radiotherapy for ankylosing spondylitis and diagnostic X-rays of the fetus in pregnancy

2) Cytotoxic drugs These, particularly alkylating agents, may induce myeloid leukaemia, usually after a latent period of several years. Exposure to benzene in industry.**Retroviruses**

One rare form of T-cell leukaemia/lymphoma appears to be associated with a retrovirus similar to the viruses causing leukaemia in cats and cattle.

4) Genetic

There is a greatly increased incidence of leukaemia in the identical twin of patients with leukaemia. Increased incidence occurs in Down's syndrome and certain other genetic disorders.

5) Immunological

Immune deficiency states (e.g. hypogammaglobulinaemia) are associated with an increase in haematological malignancy

Terminology and classification In acute leukaemia there is proliferation of primitive stem cells leading to an accumulation of blasts, predominantly in the bone marrow, which causes bone marrow failure. In chronic leukaemia the malignant clone is able to differentiate, resulting in an accumulation of more mature cells.Leukaemias are traditionally classified into four main groups:

1) acute lymphoblastic leukaemia (ALL)
2) acute myeloid leukaemia (AML)
3) chronic lymphocytic leukaemia (CLL)

4) chronic myeloid leukaemia (CML).

The diagnosis of leukaemia is usually suspected from an abnormal blood count, often a raised white count. The diagnosis is made from examination of the bone marrow. This includes the morphology of the abnormal cells, analysis of cell surface markers (immunophenotyping), clone-specific chromosome abnormalities and molecular changes. Not only does this allow an accurate diagnosis but also gives valuable prognostic information, allowing therapy to be tailored to the patient's disease.

ACUTE LEUKAEMIA

Acute leukamia - malignant tumour of the hemopoietic tissue, which morphological substrate are immature blast cells - undifferentiated or less differentiated

Normal hematopoiesis requires tightly regulated proliferation and differentiation of pluripotent hematopoietic stem cells that become mature peripheral blood cells. Acute leukemia is the result of a malignant event or events occurring in an early hematopoietic precursor. Instead of proliferating and differentiating normally, the affected cell gives rise to progeny that fail to differentiate but continue to proliferate in an uncontrolled fashion. As a result, immature myeloid cells in acute myeloid leukemia (AML), or lymphoid cells in acute lymphoblastic leukemia ALL)—often called blasts—rapidly accumulate and progressively replace the bone marrow, diminishing the production of normal red cells, white cells, and platelets. This loss of normal marrow function in turn gives rise to the common clinical complications of leukemia: anemia, infection, and bleeding. With time, the leukemic blasts pour out into the blood stream and eventually occupy the lymph nodes, spleen, and other vital organs. If untreated, acute leukemia is rapidly fatal; most patients die within several months after diagnosis. With appropriate therapy, however, the natural history of acute leukemia can be markedly altered, and many patients can be cured.

French-American-British (FAB) classification of acute leukemias:

I. Myeloid leukemia

Mo – Minimally differentiated leukemia

M1 – Myeloblastic leukemia without maturation

M2 – Myeloblastic leukemia with maturation

M3 – Hypergranular promyelocytic leukemia

M4 – Myelomonocytic leukemia

M5 – Monocytic leukemia

M6 – Erythroleukemia (DiGuglielmo's disease)

M7 – Megakaryoblastic leukemia

II. Lymphoid leukemiaL1 – Acute lymphoid leukemia, childhood variant

L2 – Acute lymphoid leukemia, adult variant

L3 – Burkitt-like acute lymphoid leukemia

The World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues divides these diseases into lineages and incorporates results from immunophenotyping, genetic and molecular analysis. The subclassification of acute leukaemias is shown below.

I. Acute myeloid leukaemia with recurrent genetic abnormalitiesAML with t(8;21) gene product AML/ETO

AML with eosinophilia inv(16) or t(16;16), gene product CBFβ/MYH11

Acute promyelocytic leukaemia t(15;17), gene product PML/RARA

AML with 11q23 abnormalities (MLL)**Acute myeloid leukaemia with multilineage dysplasia**

e.g. Following a myelodysplastic syndrome

II. Acute myeloid leukaemia and myelodysplastic syndromes, therapy-related

e.g. Alkylating agent or topoisomerase ll inhibitor

III. Acute myeloid leukaemia not otherwise specified

e.g. AML with or without differentiation, acute myelomonocytic leukaemia, erythroleukaemia, megakaryoblastic leukaemia, myeloid sarcoma

IV. Acute lymphoblastic leukaemia

Precursor B ALL

Precursor T ALL

Clinical picture

Hyperplastic syndrome (due to leukemic infiltration of tissues):

- Lyphoplastic syndrome - enlargement of lymph nodes, faucial tonsils.
- Hepatolienal syndrome – enlargement of liver and spleen.
- Osteoarticular syndrome – pain in bones and joints.
- Ulcerative-necrotic syndrome – stomatitis, gingivitis, tonsillitis.
- Neuroleucosis – focal neurological abnormalities, psychiatric desoders.
- Affection of urinary system - enlargement and infiltration of testes, enlargement of ovaries, priapism, impaired urination, haematuria, metrorrhagia.
- Affection of digestive system - dysphagia, peptic ulcer, obstruction of pyloric part of stomach, necrotizing enterocolitis.
- Affection of kidneys – proteinuria, microhaematuria, leucocyturia, acute renal failure.
- Affection of lungs - cough, haemoptysis, dyspnea, rales, respiratory failure.
- Affection of heart - myocarditis, exudative pericarditis, arrhythmias.
- Affection of endocrine system - hypopituitarism, diabetes mellitus.
- Affection of eyes - pain, photophobia, lacrimation, decreased acuity of vision.
- Affection of skin – appearance of infiltrative nodules with different color and with itching

Hemorrhagic syndrome (due to thrombocytopenia, increased permeability of vessels, impaired coagulation):

- Large skin hemorrhages, nasal, gastric, intestinal, renal, pulmonary, uterine, intracerebral hemorrhages.

Anemic syndrome (due to decreased amount of red blood cells progenitors):

- General weakness, dizziness, buzzing in the ears, darkening in the eyes, palpitation and dyspnea, paleness of skin, tachicardia, extrasystols, muted heart sounds, apical systolic murmur, nonspecific changes on ECG. Severity of anemia correlates with degree of leukemic cells proliferation in bone marrow.

Intoxicative syndrome (due to destruction of leukemic cells).

- General weakness, tiredness, sleepiness, depression, decreased appetite, loss of weight, nausea, vomiting, headache, fever, perspiration (particularly at night).

Immunodeficiency syndrome (due to significantly impaired cellular and humoral immunity related to functional inferiority of leucocytes).

- Tonsilitis, pneumonia and other infections (bacterial, viral, fungal).

The signs and symptoms of acute leukemia are usually rapid in onset, developing over a few weeks to at most a few months, and result from decreased normal marrow function and invasion of normal organs by leukemic blasts. Anemia is present at diagnosis in most patients and causes fatigue, pallor, headache, and, in predisposed patients, angina or heart failure. Thrombocytopenia is usually present, and approximately one third of patients have clinically evident bleeding at diagnosis, usually in the form of petechiae, ecchymoses, bleeding gums, epistaxis, or hemorrhage. Most patients with acute leukemia are significantly granulocytopenic at diagnosis. As a result, approximately one third of patients with AML and slightly fewer patients with ALL have significant or life-threatening infections when initially seen, most of which are bacterial in origin.

In addition to suppressing normal marrow function, leukemic cells can infiltrate normal organs. In general, ALL tends to infiltrate normal organs more often than AML does. Enlargement of lymph nodes, liver, and spleen is common at diagnosis.

Bone pain, thought to result from leukemic infiltration of the periosteum or expansion of the medullary cavity, is a common complaint, particularly in children with ALL. Leukemic cells sometimes infiltrate the skin and result in a raised, nonpruritic rash, a condition termed leukemia cutis. Leukemic cells may infiltrate the leptomeninges and cause leukemic meningitis, typically manifested by headache and nausea. As the disease progresses, central nervous system (CNS) palsies and seizures may develop. Although fewer than 5% of patients have CNS involvement at diagnosis, the CNS is a frequent site of relapse, particularly with ALL; because of the so-called blood-brain barrier, the CNS requires special therapy. Testicular involvement is also seen in ALL, and the testicles are a frequent site of relapse. In AML, collections of leukemic blast cells, often referred to as chloromas or myeloblastomas, can occur in virtually any soft tissue and appear as rubbery, fast-growing masses.

Laboratory data

Total blood analysis:

1. Normochomic normocytic anemia.
2. Reticulocytopenia.
3. Thrombocytopenia.
4. Changes of total white cells count (increasing or decreasing).
5. Blastemia.
6. Decreasing of mature neutrophils.
7. Phenomenon of “hole”.
8. Disappearing of eosinophils and basophils.
9. Increasing of ESR.

Biochemical blood analysis: increasing of γ-globulins, seromucoid, fibrin, ALT, AST, AF, bilirubin, urease and creatinin, decreasing of albumin.

Myelogram:

- Amount of blasts is increased to 30% and higher.

- Significant reduction of erythroid, granulocytic and megakariocytic hemopoetic lines.

Cytochemical, immunological, and cytogenetic investigations – allow to differentiate variants of acute leukemia

Blood examination usually shows anaemia with a normal or raised MCV. The leucocyte count may vary from as low as $1 \times 10^9/1$ to as high as $500 \times 10^9/1$ or more. In the majority of patients the count is below $100 \times 10^9/1$. Severe thrombocytopenia is usual but not invariable. The appearance of blast cells in the blood film is usually diagnostic. Sometimes the blast cell count may be very low in the peripheral blood and a bone marrow examination is necessary to confirm the diagnosis.

The bone marrow is the most valuable diagnostic investigation and will provide material for cytology, cytogenetics and immunological phenotyping. A trephine biopsy should be taken if no marrow is obtained (dry tap). The marrow is usually hypercellular, with replacement of normal elements by leukaemic blast cells in varying degrees (but more than 20% of the cells). The presence of Auer rods in the cytoplasm of blast cells indicates a myeloblastic type of leukaemia. Occasionally, in addition to the blast cell infiltrate, other findings are present, such as marrow fibrosis or bone marrow necrosis.

Instrumental investigations

Chest radiography and tomography: leukemic pneumonitis, enlarged mediastinal lymph nodes, pleural effusion.

Electrocardiography: nonspecific changes on ECG related to leukemic infiltration and myocardial dystrophy due to intoxication, anemia and toxic influence of cytostatic therapy.

Ultrasound: dilatation of heart chambers, decreasing of myocardial contractility, heterogeneity of liver and spleen structure.

Radionuclide scanning of liver: heterogeneous decreasing of isotope accumulation.

Lumbar puncture: detection of blast cells in case of neuroleucosis.

Differential diagnosis

- Leukemoid reactions.
- Aplastic anemia.
- Agranolocytosis.
- Megaloblastic anemia (differential diagnosis with acute erythromyelosis).
- Metastases of malignant tumor to bone marrow.The diagnosis of acute

leukemia is usually straightforward but can occasionally be difficult. Both leukemia and aplastic anemia can be manifested by peripheral pancytopenia, but the finding of a hypoplastic marrow without blasts usually distinguishes aplastic anemia. Occasionally, a patient has a hypocellular marrow and a clonal cytogenetic abnormality, which establishes the diagnosis of myelodysplasia or hypocellular leukemia. A number of processes other than leukemia can lead to the appearance of immature cells in the peripheral blood. Although other small round cell neoplasms can infiltrate the marrow and sometimes mimic leukemia, immunologic markers are effective in differentiating the two. Leukemoid reactions to infections such as tuberculosis can result in the outpouring of large numbers of young myeloid cells, but the proportion of blasts in marrow or peripheral blood almost never reaches 20% in a leukemoid reaction. Infectious mononucleosis and other viral illnesses can sometimes resemble ALL, particularly if large numbers of atypical lymphocytes are present in the peripheral blood and if the disease is accompanied by immune thrombocytopenia or hemolytic anemia.

Management

With the development of effective programs of combination chemotherapy and advances in hematopoietic stem cell transplantation, many patients with acute leukemia can be cured. These therapeutic measures are complex and are therefore best carried out at centers with appropriate support services and experience in treating leukemia. Because leukemia is a rapidly progressive disease, specific

antileukemic therapy should be started as soon after diagnosis as possible, usually within 48 hours. The goal of initial chemotherapy is to induce a CR with restoration of normal marrow function. In general, induction chemotherapy is intensive and is accompanied by significant toxicities. Therefore, patients should be stabilized to the extent possible before specific antileukemic therapy is begun.

Treatment of acute leukemia (program):

1. Curative regimen.
2. Cytostatic therapy.
3. Desintoxicative therapy.
4. Prevention of blastic lysis.
5. Immunotheraphy.
6. Bone marrow transplantation.
7. Treatment of infectious complications.
8. Treatment of anemia.
9. Treatment of hemorrhagic syndrome.
10. Treatment of cytostatic desease.

The first decision must be whether or not to give specific treatment. This is generally aggressive, has a number of side-effects, and may not be appropriate for the very elderly or patients with other serious disorders. In these patients supportive treatment only should be offered; this can effect considerable improvement in well-being.The aim of treatment is to destroy the leukaemic clone of cells without destroying the residual normal stem cell compartment from which repopulation of the haematopoietic tissues will occur. There are three phases:

Remission induction. In this phase, the bulk of the tumour is destroyed by combination chemotherapy. The patient goes through a period of severe bone marrow hypoplasia, requiring intensive support and inpatient care from specially trained medical and nursing staff.

Remission consolidation. If remission has been achieved by induction therapy, residual disease is attacked by therapy during the consolidation phase. This consists of a number of courses of chemotherapy, again resulting in periods of

marrow hypoplasia. In poor prognosis leukaemia this may include a stem cell transplant.

Remission maintenance. If the patient is still in remission after the consolidation phase for acute lymphoblastic leukaemia, a period of maintenance therapy is given, consisting of a repeating cycle of drug administration. This may extend for up to 3 years if relapse does not occur and is usually given on an outpatient basis. Thereafter, specific therapy is discontinued and the patient observed. (This maintenance phase is not thought to be of benefit in most patients with AML who have been brought into complete remission by induction and consolidation therapy.)Treatment of acute leukemia (medications)

Induction of remission in acute lymphocytic leukemia:

- Vincristine (0,1% 1 ml) by 2 ml (2 mg) daily i/v
- Prednisolone (0,005 g) by 60 mg/m^2 daily per os
- L-asparaginase (10000 IU) by 6000 IU/m^2 daily i/v
- Rubomycin 50mg/m^2 daily i/v

Supporting therapy:

- Mercaptopurine 60 mg/m^2 daily per os
- Methotrexate 20 mg/m^2 1 time in a week per os

Induction of remission in acute myeloid leukemia «7+3»:

- Cytarabine (1000 mg in a vial) 100 mg/m^2 2 times in a day i/v
- Rubomycin 45 mg/m^2 daily i/v

Supporting therapy:

- Cytarabine (1000 mg in a vial) 100 mg/m^2 2 times in a day i/v

Cyclophosphamide (1000 mg in a vial) 1000 mg/m^2 in a day i/vExisting infections identified and treated (e.g. urinary tract infection, oral candidiasis, dental, gingival and skin infections). Prophylaxis against systemic fungal infections with either fluconazole or itraconazole is usual practice during intensive chemotherapy.

Fever (> 38°C) lasting over 1 hour in a neutropenic patient (absolute neutrophil count < 1.0×10^9/l) indicates possible septicaemia. Parenteral broad-

spectrum antibiotic therapy is essential. Empirical therapy is given with a combination of an aminoglycoside (e.g. gentamicin) and a broad-spectrum penicillin (e.g. piperacillin/tazobactam). This combination is synergistic and bactericidal and should be continued for at least 3 days after the fever has resolved.

Herpes simplex infection occurs frequently round the lips and nose during ablative therapy for acute leukaemia and is treated with aciclovir. This may also be prescribed prophylactically to patients with a history of cold sores or elevated titres to herpes simplex. Herpes zoster manifesting as chicken pox or, after reactivation, as shingles should be treated in the early stage with high-dose aciclovir as this can be fatal in immunocompromised patients.

Anaemia corrected with red cell concentrate infusion to maintain level of hemoglobin > 100 g/l. Thrombocytopenic bleeding requires platelet transfusions unless the bleeding is trivial. Prophylactic platelet transfusion should be given to maintain the platelet count above 10×10^9/l. Coagulation abnormalities occur and need accurate diagnosis and treatment as appropriate, usually with fresh frozen plasma. If possible, central venous catheter inserted to facilitate access to the circulation for delivery of chemotherapy. Therapeutic regimen carefully explained to the patient and informed consent obtained.Cellular breakdown during induction therapy increases uric acid production, which may cause renal failure. Allopurinol and intravenous hydration are given to try to prevent this, along with close monitoring of biochemistry. Occasionally dialysis may be required.

Traditionally, blood and marrow transplantation (BMT) has offered the only hope of 'cure' in a variety of haematological disorders. The type of transplant is defined according to donor and source of stem cell. In allogeneic BMT the stem cells come either from a related (usually an HLA-identical sibling) donor or from a closely HLA-matched volunteer unrelated donor (VUD). In an autologous transplant the stem cells are harvested from the patient and stored in the vapour phase of liquid nitrogen until required. Stem cells can be harvested from the bone marrow or from the blood.

General indications for allogeneic bone marrow transplantation:

- Neoplastic disorders affecting the totipotent or pluripotent stem cell compartment (e.g. leukaemias)
- Those with a failure of haematopoiesis (e.g. aplastic anaemia)
- A major inherited defect in blood cell production (e.g. thalassaemia, immunodeficiency diseases)
- Inborn errors of metabolism with missing enzymes or cell lines

Psychological support is a key aspect of care. Patients should be kept informed, and their questions answered and fears allayed as far as possible. An optimistic attitude from the staff is vital. Delusions, hallucinations and paranoia are not uncommon during periods of severe bone marrow failure and septicaemic episodes, and should be met with patience and understanding.

Prognosis

Without treatment the median survival of patients with acute leukaemia is about 5 weeks. This may be extended to a number of months with supportive treatment. Patients who achieve remission with specific therapy have a better outlook. Around 80% of adult patients under 60 years of age with ALL or AML achive remission. Remission rates are lower for older patients. However, the relapse rate continues to be high.

CHRONIC LEUKAEMIA

Chronic leukemia – malignant tumor of hemopoetic tissue, which morphologic substrate are mature sufficiently defferentiated cells.**Chronic myeloid leukemia (CML)** – malignant tumor of hemopoetic tissue, which morpologic subsrate are myeloid cells, predominantly - granulocytes.

Etiology and pathogenesis of chronic myeloleukosis

At present time the only evident etiologic factor is ionizing radiation.

Approximately 95% of patients with CML have a chromosome abnormality known as the Philadelphia (Ph) chromosome. This is a shortened chromosome 22 and is the result of a reciprocal translocation of material with chromosome 9. The

break on chromosome 22 occurs in the breakpoint cluster region (BCR). The fragment from chromosome 9 that joins the BCR carries the *abl* oncogene, which forms a chimeric gene with the remains of the BCR. This *BCR ABL* chimeric gene codes for a 210 kDa protein with tyrosine kinase activity, which plays a causative role in the disease, influencing cellular proliferation, differentiation and survival. In some apparently Ph chromosome-negative patients, the BCR ABL gene product is detectable by molecular techniques.

Clinical picture of chronic myeloid leukemia

About 25% of patients are asymptomatic at diagnosis. On examination the principal clinical finding is splenomegaly, which is present in 90% of patients. In about 10% the enlargement is massive, extending to over 15 cm below the costal margin. A friction rub may be heard in cases of splenic infarction. Hepatomegaly occurs in about 50% of patients. Lymphadenopathy is unusual.

The symptoms of CML, when present, are due to anemia and splenomegaly: fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain. Rarely, bleeding (associated with a low platelet count and/or platelet dysfunction) or thrombosis (associated with thrombocytosis and/or marked leukocytosis) occur. Other rare presentations include gouty arthritis (from elevated uric acid levels), priapism (usually with marked leukocytosis or thrombocytosis), retinal hemorrhages, and upper gastrointestinal ulceration and bleeding (from elevated histamine levels due to basophilia). Headaches, bone pain, arthralgias, pain from splenic infarction, and fever are uncommon in the chronic phase but more frequent as CML progresses. Leukostatic symptoms, such as dyspnea, drowsiness, loss of coordination, or confusion, which are due to sludging in the pulmonary or cerebral vessels, are uncommon in the chronic phase, but these symptoms appear more frequently in the accelerated or blastic phases.

1. **Initial period:** usually complaints are absent, sometimes – general weakness, tiredness, perspiration at night, dull pain in left hypochondrial region, at physical examination – spleen is slightly enlarged.

2. **Period of obvious clinical manifestations (chronic stable phase):** complents on general weakness, tiredness, perspiration at night, pain in bones, pain in the left hypochonrial region, increasing of body temperature, at physical examination – paleness of skin and mucous membranes, painless enlargement of lymph nodes, enlargement of spleen and less prominent enlargement of liver. Leukemic infiltration of tissues may lead to different clinical symptoms related to affection of different organs and systems.
3. **Terminal period (phase of acceleration and blastic crisis):** all clinical symptoms significantly increase. Clinical picture become similar to acute leukemia.

Laboratory data in chronic myeloid leukemia

Initial period.

Total blood analysis:

- Leucocytosis to 15-20×10^9/L
- Left shift of leucocytic formula with appearance of myelocytes
- Increasing of basophills and eosinophils (basophilic-eosinophilic association)

Myelogram: increasing of cells from myelocytic line with shift to the left

Period of obvious clinical picture (chronic stable phase).

Total blood analysis:

- Leucocytosis to 50-300×10^9/L
- Left shift of leucocytic formula to single blasts.
- Basophilic-eosinophilic association
- Thrombocytosis to 600-1000×10^9/L (in most patients)
- Lymphopenia
- Normochromic anemia

Myelogram: significant increasing of cells from myelocytic line.

Cytogenetic analysis: in 90% of patients the Philadelphic chromosome is found in all blood cells except T-lymphocytes.

Biochemical analysis: increasing of uric acid, vitamin B12, lactatedehydrogenase, potassium, calcium, decreasing of cholesterol and glucose.

Terminal period (phase of acceleration and blastic crisis):

- Increasing of blast cells >30% in peripheral blood or bone marrow.

Instrumental investigations in chronic myeloid leukemia

- Chest radiography: leukemic and inflammatory infiltration of lungs
- Ultrasound: enlargement of heart, liver, spleen.
- ECG: nonspecific diffuse changes in myocardium, atrio-ventricular block**Differential diagnosis**

1. Idiopathic myelofibrosis
2. Polycythemia
3. Essential thrombocytosis
4. Leukemoid reactions
5. Acute leukemia (differential diagnosis in the phase of blastic crisis)

CML must be differentiated from leukemoid reactions, which usually produce WBC counts lower than 50×10^9/L, toxic granulocytic vacuolation, absence of basophilia and a clinical history and physical examination suggesting the origin of the leukemoid reaction. Corticosteroids can rarely cause extreme neutrophilia with a left shift, but this abnormality is self-limited and of short duration.

CML may be more difficult to differentiate from other myelodysplastic or myeloproliferative syndromes. Patients with agnogenic myeloid metaplasia with or without myelofibrosis frequently have splenomegaly, neutrophilia, and thrombocytosis. Polycythemia rubra vera with associated iron deficiency, which causes normal hemoglobin and hematocrit values, can manifest with leukocytosis and thrombocytosis. Such patients usually have WBC count less than 25×10^9/L, and no Ph chromosome.

The greatest diagnostic difficulty lies with patients who have splenomegaly and leukocytosis but do not have the Ph chromosome.

Treatment of chronic myeloid leukemia (program)

1. Cytostatic therapy

2. Treatment by α_2-interferon
3. Radiotherapy
4. Leucopheresis
5. Spleenectomy
6. Symptomatic treatment
7. Transplantation of bone marrow

Cytostatic therapy of chronic myeloid leukemia

Monotherapy.

1. Drug of choice – imatinib "Glivec" (100 mg in 1 tab) by 400 mg 1 time in a day per os at chronic phase and by 600-800 mg 1 time a day in phase of acceleration and blastic crisis.
2. Alternative – hydroxycarbomide "Hydroxyurea" (500 mg in 1 tab) by 30 mg/kg in a day per os.
3. Alternative - busulfan "Myelosanum" (2 mg in 1 tab) by 2-6 mg in a day per os.

Polychemotherapy

Program «7+3»:

Cytarabine (1000 mg in a vial) 100 mg/m^2 2 times in a day i/v

Rubomycin 45 mg/m^2 in a day i/v

Chronic lymphocytic leukemia (CLL) – variant of leukemia with affection of lymphocytic line, which morphological substrate are mature but functionally defective lymphocytes. The cells accumulate in the bone marrow, lymph nodes, liver, spleen, and occasionally other organs.

Etiology and pathogenesis of chronic lymphocytic leukemia

The cause of CLL is unknown. Ionizing radiation and viruses have not been associated with CLL, although recently hepatitis C infection has been associated with splenic lymphoma with villous lymphocytes (another indolent B-cell disorder). Familial clustering in CLL is more common than in other leukemias; first-degree relatives of patients have a two- to four-fold higher risk and develop

CLL at a younger age, compared with the general population (anticipation). Farmers have a higher incidence of CLL than do those in other occupations, raising the question of the possible etiologic role of herbicides or pesticides. No definite leukemogenic role of chemicals, including benzene, has been established for CLL.

Recently, genetic predisposition and retroviruses are considered as etiological factors of chronic lymphocytic leukemia. The influences of etiological factors lead to different mutations in cells-precursors of B- and T-lymphocytes. The pathological clone of lymphocytes further progresses, but less rapidly then in case of acute leukemia. The lymphocytes in chronic lymphocytic leukemia are functionally defective – with decreased synthesis of immunoglobulines.

Clinical picture of chronic lymphocytic leukemia

The onset is very insidious. Indeed, in around 70% of patients the diagnosis is made incidentally on a routine full blood count.

Most patients with CLL are asymptomatic. Symptoms such as fatigue, lethargy, loss of appetite, weight loss, and reduced exercise tolerance are nonspecific. Many patients have enlarged lymph nodes. B symptoms (fever, night sweats, weight loss) are rarely present initially, and their presence in later stages of the disease suggests transformation to large cell lymphoma. The most common infections are sinopulmonary. As the disease progresses, the frequency of neutropenia, T-cell deficiency, and hypogammaglobulinemia increases, resulting in infections with gram-negative bacteria, fungi, and viruses such as herpes zoster and herpes simplex.

The major physical findings relate to infiltration of the reticuloendothelial system. Lymphadenopathy with discrete, rubbery, mobile lymph nodes is present in two thirds of patients at diagnosis. Later, as the lymph nodes enlarge, they can become matted. Enlargement of the liver or spleen is less common at diagnosis (approximately 10% and 40% of cases, respectively) but occurs more frequently with progression. Organ failure resulting from infiltration with CLL is uncommon. Infiltration of the central nervous system in CLL is rare, and central nervous

system symptoms are more likely to be caused by opportunistic infections, such as cryptococcosis or listeriosis.

Initial period: complaints – usually absent, sometimes general weakness, perspiration, signs of "respiratory infection", at physical examination – painless enlarged lymph nodes (on neck, in axillary regions, latter – in other regions).

Period of obvious clinical manifestations: complaints – on severe general weakness, tiredness, significant perspiration especially at night, loss of weight, fever, at physical examination – generalized enlargement of lymph nodes, nonspecific skin lesions (herpes, erythrodermia, nettle rash, fungal lesions), enlargement of spleen and liver. Leukemic infiltration may produce nonspecific changes in different organs and systems.

Terminal period: progressive worsening of general patient's state with accompanying anemia, intoxication and exhaustion. The most frequent complications are severe generalized infection, renal failure, neuroleukemia, cardiopathy, respiratory failure, blastic crisis**Laboratory data in chronic lymphocytic leukemia**

1. Initial period.

Total blood analysis: leucocytosis to 50×10^9/L; lymphocytosis 60-80%.

2. Period of obvious clinical manifestations.

Total blood analysis: leucocytosis to $50\text{-}200\times10^9$/L; lymphocytosis 80-90%; Botkin-Humprecht's cells (partially destroyed nucleus of lymphocytes in the blood smear); normochromic normocytic anemia; thrombocytopenia; elevated ESR.

Myelogram: elevated lymphocytes (>30% of total amount of myelocaryocytes).

Biochemical blood analysis: hypogammaglobulinemia, elevation of AST and ALT, elevation of conjugative and nonconjugative bilirubin

Total urine analysis: proteinuria, microhematuria.

Immunological analysis: elevation of mature B-lymphocytes, decreasing of immunoglobulines (IgA, IgM, IgG).

Cytochemical analysis: elevation of glycogen in lymphocytes of peripheral blood and bone marrow.

Cytogenetic analysis: different chromosomal anomalies are detected in 65% patients

3. Terminal period.

Severe anemia; elevation of blasts >30% in peripheral blood or bone marrow (blastic crisis)

Instumental investiogations in chronic lymphocytic leukemia:

Ultrasound or computed tomography (in case of insufficient visualization): enlargement of spleen, liver and lymph nodes of abdominal cavity.

Differential diagnosis in chronic lymphocytic leukemia

1. Lymphomas.
2. Lymphogranulematosis (Hodgkin's disease).
3. Leukemoid reactions.
4. Acute leukemia.

The many diseases that can cause lymphocytosis, such as pertussis (Chapter 334), cytomegalovirus (Chapter 399), Epstein-Barr virus mononucleosis (Chapter 400), tuberculosis (Chapter 345), toxoplasmosis (Chapter 370), chronic inflammatory disorders, and autoimmune syndromes, are seldom confused with B-cell CLL, largely because the lymphocytosis in these conditions is usually less than 15,000/μL and is not sustained. If doubt persists, immunophenotypic or molecular studies can distinguish the monoclonal lymphocytosis in CLL from the T-cell or polyclonal B-cell proliferation in the other disorders.

Treatment of chronic lymphocytic leukemia.

1. Curative regimen.

2. Cytostatic therapy. Early treatment by cytostatics does not increase the duration of life. That is why treatment starts only at period of obvious clinical manifestations. Treatment is only required if there is evidence of bone marrow failure, massive or progressive lymphadenopathy or splenomegaly, systemic

symptoms such as weight loss or night sweats, a rapidly increasing lymphocyte count or autoimmune cytopenias.

Monotherapy.

The drug of choice is fludarabine “Fludara” (50 mg in a vial) by 25 mg/m^2 1 time in a day in 100 ml of isotonic solution of sodium chloride i/v

Traditional medication for treatment - chlorambucil «Leukeran» (2 mg in 1 tab) by 2 tab 1-3 time in a day per os.

Polychemotherapy:

cyclophosphamide (240 mg/m^2 daily), methotrexate (12 mg/m^2 daily), vincristine (1,5 mg/m^2 daily), mercaptopurine (60 mg/kg daily), prednisolone (60 mg daily).

3. Curative lymphocytopheresis.

4. Radiotherapy.

5. Spleenectomy.

6. Treatment by glucocorticoids.

7. Treatment of infectious complications. Supportive care is increasingly required in progressive disease, e.g. transfusions for symptomatic anaemia or thrombocytopenia, prompt treatment of infections and for some patients with hypogammaglobulinaemia, immunoglobulin replacement. Radiotherapy may be used for lymph nodes causing discomfort or local obstruction, and for symptomatic splenomegaly. Splenectomy may be required to improve low blood counts due to autoimmune destruction or to hypersplenism, and can relieve massive splenomegaly. **CASE-BASED QUESTIONS.Task 1**

A 60-year-old asymptomatic man is found to have a leukocytosis when a routine CBC is obtained. Physical exam shows no abnormalities. The spleen is of normal size. Lab data includes:

Hgb: 90 g/L (normal 140 to 180 g/L)

Leukocytes: 40×10^9/L (normal 4,3 to $10,8\times10^9$/L)

Peripheral blood smear shows a differential that includes 97% small lymphocytes.

The most likely diagnosis is

A. Acute monocytic leukemia

B. Chronic myelogenous leukemia

C. Chronic lymphocytic leukemia

D. Tuberculosis

Task 2

This patient will require chemotherapy

A. If the white blood cell count rises

B. If lymphadenopathy develops

C. To control anemia or thrombocytopenia

D. Only when acute lymphocytic leukemia develops

Task 3

Which of the following statements regarding polycythemia vera is correct?

A. An elevated plasma erythropoietin level excludes the diagnosis.

B. Transformation to acute leukemia is common.

C. Thrombocytosis correlates strongly with thrombotic risk.

D. Aspirin should be prescribed to all these patients to reduce thrombotic risk.

E. Phlebotomy is used only after hydroxyurea and interferon have been tried.

Task 4

A patient with acute lymphoid leukemia (ALL) is admitted with respiratory distress and chest pain. The patient reports 1 day of shortness of breath not associated with cough. There have been no sick contacts, and before the onset of the respiratory symptoms, the patient only recalls fatigue. A chest radiograph shows faint diffuse interstitial infiltrates without pulmonary edema. The cardiac silhouette is normal. An arterial blood gas shows a PaO2 = 54 mmHg, while the pulse oximetry is 97% on room air. A carbon monoxide level is normal. All of the following laboratory abnormalities are expected in this patient *except*

A. bcr-abl mutation

B. blast count >100×10^9/L

C. elevated lactate dehydrogenase levels

D. increased blood viscosity

E. methemoglobinemia

Task 5

The evaluation in a newly diagnosed case of acute lymphoid leukemia (ALL) should routinely include all of the following *except*

A. bone marrow biopsy

B. cell-surface phenotyping

C. complete metabolic panel

D. cytogenetic testing

E. lumbar puncture

F. plasma viscosity

Task 6

A 50-year-old female presents to your clinic for evaluation of an elevated platelet count. The latest complete blood count is white blood cells (WBC) 7×10^9/L, hematocrit 34%, and platelets 600×10^9/L. All the following are common causes of thrombocytosis *except*

A. iron-deficiency anemia

B. essential thrombocytosis

C. chronic myeloid leukemia

D. myelodysplasia

E. pernicious anemia

Task 7

You are seeing a patient in follow-up in whom you have begun an evaluation for an elevated hematocrit. You suspect polycythemia vera based on a history of

aquagenic pruritus and splenomegaly. Which set of laboratory tests are consistent with the diagnosis of polycythemia vera?

A. Elevated red blood cell mass, high serum erythropoietin levels, normal oxygen saturation

B. Elevated red blood cell mass, low serum erythropoietin levels, normal oxygen saturation

C. Normal red blood cell mass, high serum erythropoietin levels, low arterial oxygen saturation

D. Normal red blood cell mass, low serum erythropoietin levels, low arterial oxygen saturation

Task 8

A 64-year-old man with chronic lymphoid leukemia (CLL) and chronic hepatitis C presents for his yearly follow-up. His white blood cell count is stable at 83×10^9/L, but his hematocrit has dropped from 35% to 26% and his platelet count also dropped from 178×10^9/L to 69×10^9/L. His initial evaluation should include all of the following *except*

A. AST, ALT, and prothrombin time

B. bone marrow biopsy

C. Coombs test

D. peripheral blood smear

E. physical examination

Task 9

A 48-year-old woman is admitted to the hospital with anemia and thrombocytopenia after complaining of profound fatigue. Her initial hemoglobin is 85 g/L, hematocrit 25.7%, and platelet count 42×10^9/μL. Her leukocyte count is $9{,}54\times10^9$/L, but 8% blast forms are noted on peripheral smear. A chromosomal analysis shows a reciprocal translocation of the long arms of chromosomes 15 and

17, t(15;17), and a diagnosis of acute promyelocytic leukemia is made. The induction regimen of this patient should include which of the following drugs:

A. All-*trans*-retinoic acid (ATRA, or triretinoin)

B. Arsenic

C. Cyclophosphamide, daunorubicin, vinblastine, and prednisone

D. Rituximab

E. Whole-body irradiation

Task 10

All of the following statements regarding the epidemiology of and risk factors for acute myeloid leukemias are true *except*

A. Anticancer drugs such as alkylating agents and topoisomerase II inhibitors are the leading cause of drug-associated myeloid leukemias.

B. Individuals exposed to high-dose radiation are at risk for acute myeloid leukemia whereas individuals treated with therapeutic radiation are not unless they are also treated with alkylating agents.

C. Men have a higher incidence of acute myeloid leukemia than women.

D. The incidence of acute myeloid leukemia is greatest in individuals <20 years.

E. Trisomy 21 (Down syndrome) is associated with an increased risk of acute myeloid leukemia.

Further reading:

1. Principles of Harrison's internal medicine, self-assessment and board review 18th editon /Edited by Charles Wiener etc. - The McGraw-Hill Professional. – 2012. – 514 p.
2. Board review from Medscape. Case-based internal medicine self-assessment questions / Editor-in-Chief David C. Dale. - WebMD. – 2005. – 592 p.

3. Kaplan Medical USMLE Step 2 Clinical Knowledge Qbook, 5th edition/ Edited by Kaplan inc. – Kaplan Publishing. – 2011. - 540 p.
4. Harrison's principles of internal medicine, 18th Edition / Edited by Dan Longo, Anthony S. Fauci etc. - The McGraw-Hill Professional. – 2011. - 4012 p.
5. Davidson's Principles and Practice of medicine, 21st edition / Edited by Nicki R. Colledge, Brian R. Walker, Stuart H. Relston. - Churchill Livingstone – 2010. – 1376 p.
6. Goldman's Cecil Medicine, 24th edition / Edited by Lee Goldman, Andrew I. Schafer. – Saunders Ltd. – 2011. – 2672 p.
7. Kumar & Clark's Clinical Medicine, 8th edition / Edited by Parveen Kumar, Michael Clark. – Saunders Ltd. – 2012. – 1304 p.
8. ESMO Clinical Practice Guidelines: Hematologic Malignancies. Available at: http://www.esmo.org/education-research/esmo-clinical-practice-guidelines/topics/hematologic-malignancies.html