Міністерство охорони здоров'я України
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ЗАТВЕРДЖЕНО
на засіданні кафедри внутрішньої медицини №3
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Зав. кафедри _____д.мед.н., професор Л.В. Журавльова

МЕТОДИЧНІ ВКАЗІВКИ
для студентів

з дисципліни «Внутрішня медицина (в тому числі з ендокринологією)
студенти 4 курсу I, II, III медичних факультетів, V та VI факультетів по підготовці іноземних студентів

Хронічні лейкози

Харків 2016

«Chronic leukemia»

Topicality

The incidence of all types of leukemia is 13 cases per 100,000 of population per year. Acute leukemia composes 1-2% of all cases of new malignancies annually. In general, men are affected more often than women. Caucasians are getting sick with leukemia more often than any other ethnic groups. There are some differences between types of leukemia depending on the age of patients.

The incidence of chronic myelogenous leukemia is 1-1,7 per 100,000 of population and ranks fifth among the most common leukemias in adults. The peak incidence is observed in the age of 40-50.

Chronic lymphocytic leukemia is the most common type of leukemia diagnosed in adults. The incidence of chronic lymphocytic leukemia is an average of 3.3 per 100,000 of population, while in people over 65 it increases to 20 per 100,000 of population. The average age of patients at the time of diagnosis of the disease is 64 years.

The topicality of early diagnosis and treatment of leukemia stems from the difficulty in conducting medical and psychological support for patients with these diseases.

Learning Objectives:

- provide the definition for chronic leukemia;
- to acquaint students with the etiology and pathogenesis of different types of chronic leukemia;
- to acquaint students with the modern classification of chronic leukemia;
- to teach students to recognize the major symptoms and syndromes in chronic leukemia;
- to acquaint students with the research methods used for the diagnosis of chronic leukemia; indications and contraindications for their use; methods of their implementation; diagnostic value of each of them;
- to teach students independently interpret the results of studies;
- to train students to recognize certain types of chronic leukemia;
- to teach students to prescribe treatment for chronic leukemia.

What should a student know?

- main etiological factors and pathogenetic mechanisms of chronic leukemia;
- main clinical syndromes of chronic leukemia;
- complaints and physical examination data in chronic leukemia;
- methods of physical examination of patients with chronic leukemia;
- diagnostic value of complete blood count and myelogram in chronic leukemia;
- diagnostic value of the molecular biology data, cytochemical, cytogenetic and immunophenotyping assays;
- sternal puncture: diagnostic value, indications, contraindications;
- diagnostic value of bone marrow trepanobiopsy: indications, contraindications;
- list of additional research tools that are used to detect splenomegaly, hepatomegaly, increased internal lymph nodes, leukemic infiltrates in various organs and tissues;
- complications of chronic leukemia;
- management of patients with chronic leukemia;
- treatment of chronic leukemia (pharmacological treatment, chemotherapy, radiotherapy, stem cells transplantation)
- measures to prevent leukemia development.

What should a student be able to do?

- to define key clinical syndromes of chronic leukemia;

- to set inspection program for patient with chronic leukemia;
- to interpret the results of laboratory tests;
- to perform differential diagnosis of chronic leukemia;
- to prescribe treatment for patients with chronic leukemia;
- to evaluate the prognosis of patients.

The list of practical skills which should be acquired by a student:

- examination of skin and its derivatives, visible mucous membranes;
- palpation of peripheral lymph nodes;
- examination of the abdomen;
- superficial palpation of the abdomen;
- deep methodical sliding palpation of the abdomen by Obraztsov-Strazhesko;
- percussion and palpation of the liver and spleen.

Topic content.

Hematopoiesis is the process by which the formed elements of blood are produced. The process is regulated through a series of steps beginning with the hematopoietic stem cell. Stem cells are pluripotent and capable of producing any type of blood cell (red cells, all classes of granulocytes, monocytes, platelets and the cells of the immune system). The precise molecular mechanism either intrinsic to the stem cell itself or through the action of extrinsic factors by which the stem cell becomes committed to a given Iineage is not fully defined.

Myelopoiesis is the formation of all formal blood cells, except lymphocytes. Lymphopoiesis is the formation of lymphocytes (B and T cells). According to the number of formal blood elements there are 6 lineages of myelopoiesis and 2 lineages of lymphopoiesis. Every lineage of differentiation contains 6 types of cells:

1. stem cells (pluripotent)
2. colony-forming units (partly determined)
3. unipotent stem cells (give rise to a specific cell lineage)
4. blasts (immature cells that have no morphological differences, but can be differentiated in one direction)
5. intermediate cells (maturing cells that already have morphological differences)
6. mature cells

The central organs of hematopoiesis are bone marrow and thymus. Localization of bone marrow is spongy substance of spongy and flat bones, and long bones diaphyses. Thymus is localized behind the sternum and is responsible for proliferation and maturation of T lymphocytes.

Leukocytes - the major cells comprising inflammatory and immune responses include granulocytes (neutrophils, eoinophils, basophils) and agranulocytes (lymphocytes, monocytes). The main function of granulocytes is phagocytosis. The main function of agranulocytes is provision of humoral and cellular immunity. Leukocyte maturation in the marrow is under the regulatory control of a number of different factors known as colony-stimulating factors (CSFs) and interleukins (ILs).

The leukemias are cancers of the white blood cells (WBCs) involving bone marrow, circulating WBCs, and organs such as the spleen and lymph nodes.

Chronic leukemias are the malignant tumors of hematopoietic tissue, which consist mainly of mature cells that achieved certain level of differentiation. They usually manifest as abnormal leukocytosis with or without cytopenia in an otherwise asymptomatic person. Findings and management differ significantly between chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML).

Classification of chronic leukemia

I. Chronic leukemia of myelogenous origin:

¬ Chronic myelogenous leukemia.

¬ chronic monocytic and myelomonocytic leukemia.

¬ Idiopathic myelofibrosis.
¬ Essential thrombocytosis.
¬ polycythemia vera (erythremia).
¬ myelodysplastic syndrome.
II. Chronic lymphoproliferative diseases:
¬ Chronic lymphocytic leukemia.
¬ Paraproteinemic hemoblastosis (multiple myeloma, Waldenstrom's macroglobulinemia).
¬ Lymphoma and lymphosarcoma.

CHRONIC MYELOID LEUKEMIA

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder, which involves cells of myelogenous lineage, mainly granulocytes.

Etiology. There are no familial associations in CML. Exposure to ionizing radiation (eg. nuclear accidents, radiation treatment for ankylosing spondylitis or cervical cancer) has increased the risk of CML, which peaks at 5- 10 years after exposure and is dose-related.

Pathophysiology. The disease is driven by the BCR-ABLl chimeric gene product, a constitutively active tyrosine kinase, resulting from a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11.2), cytogenetically detected as the Philadelphia chromosome (Ph), which is present in more than 90% of classical CML cases. This BCR-ABLl oncoprotein exhibits constitutive kinase activity that leads to excessive proliferation and reduced apoptosis of CML cells, endowing them with a growth advantage over their normal counterparts. Although granulocyte production predominates, the neoplastic clone includes RBCs, megakaryocytes, monocytes. Over time, normal hematopoiesis is suppressed, but normal stem cells can persist and may reemerge following effective therapy.

Clinical presentation. CML has 3 phases:

- **Chronic phase** : An initial indolent period that may last months to years
- **Accelerated phase** : Treatment failure, worsening anemia, progressive thrombocytopenia or thrombocytosis, persistent or worsening splenomegaly, clonal evolution, increasing blood basophils, and increasing marrow or blood blasts
- **Blast phase** : Accumulation of blasts in extramedullary sites (eg, bone, CNS, lymph nodes, skin), blasts in blood or marrow increased to > 20%. The blast phase leads to fulminant complications resembling those of acute leukemia, including sepsis and bleeding. Some patients progress directly from the chronic to the blast phase.

Most patients with CML (90%) present in the chronic phase. Depending on the timing of diagnosis, patients are often asymptomatic (if the diagnosis is discovered during healthcare screening tests). Common symptoms, when present, are manifestations of anemia and splenomegaly. These may include fatigue, malaise, weight loss (if high leukemia burden), or early satiety and left upper quadrant pain or masses (from splenomegaly). Less common presenting findings include thrombotic or vasoocclusive events (from severe leukocytosis or thrombocytosis). These include priapism, cardiovascular complications, myocardial infarction, venous thrombosis, visual disturbances, dyspnea and pulmonary insufficiency, drowsiness, loss of coordination, confusion, or cerebrovascular accidents. Bleeding diatheses findings include retinal hemorrhages, gastrointestinal bleeding and others. Patients who present with, or progress to the accelerated or blastic phases have additional symptoms including unexplained fever, significant weight loss, severe fatigue, bone and joint aches, bleeding and thrombotic events, and infections.

Splenomegaly is the most common physical finding, occurring in 20-70% of patients depending on health care screening frequency. Other less common findings include hepatomegaly (10-20%), lymphadenopathy (5-10%), and extramedullary disease (skin or

subcutaneous lesions). The latter indicates CML transformation if a biopsy confirms the presence of sheets ofblasts. Other physical findings are manifestations of complications of high tumor burden (e.g. cardiovascular, cerebrovascular, bleeding). High basophil counts may be associated with histamine overproduction causing pruritus, diarrhea, flushing, and even gastrointestinal ulcers.

Diagnosis

- CBC and peripheral smear
- Bone marrow examination
- Cytogenetic studies (Ph chromosome)

CML is most frequently diagnosed by a CBC obtained incidentally or during evaluation of splenomegaly. Granulocyte count is elevated, usually < 50,000/μL in asymptomatic patients and 200,000/μL to 1,000,000/μL in symptomatic patients. Platelet count is normal or moderately increased. Hb level is usually > 10 g/dL.

Peripheral smear may help differentiate CML from leukocytosis of other etiology. In CML, peripheral smear frequently shows immature granulocytes as well as absolute eosinophilia and basophilia, although in patients with WBC counts < 50,000/μL, immature granulocytes may not be seen. Leukocytosis in patients with myelofibrosis is usually associated with nucleated RBCs, teardrop-shaped RBCs, anemia, and thrombocytopenia. Leukemoid reactions resulting from cancer or infection are not often associated with absolute eosinophilia and basophilia.

The leukocyte alkaline phosphatase score is usually low in CML and increased in leukemoid reactions. Bone marrow examination should be done to evaluate the karyotype as well as cellularity and extent of myelofibrosis.

Diagnosis is confirmed by finding the Ph chromosome in samples examined with cytogenetic or molecular studies, although it is absent in 5% of patients. Techniques such as fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) are now used to aid in the diagnosis of CML. They are more sensitive approaches to estimate the CML burden in patients on tyrosine kinase inhibitor (TKI) therapy. They can be done on peripheral samples and thus are less painful and more convenient. Patients with CML at diagnosis should have a FISH analysis to quantify the percentage of Ph-positive cells, if FISH is used to replace marrow cytogenetic analysis in monitoring response to therapy. FISH may not detect additional chromosomal abnormalities (c1onal evolution); thus, a cytogenetic analysis is usually recommended at the time of diagnosis.

During the accelerated phase of disease, anemia and thrombocytopenia usually develop. Basophils may increase, and granulocyte maturation may be defective. The proportion of immature cells and the leukocyte alkaline phosphatase score may increase. In the bone marrow, myelofibrosis may develop and sideroblasts may be seen on microscopy. Evolution of the neoplastic clone may be associated with development of new abnormal karyotypes, often an extra chromosome 8 or isochromosome 17.

Further evolution may lead to a blast phase with myeloblasts (60% of patients), lymphoblasts (30%), and megakaryoblasts (10%). In 80% of these patients, additional chromosomal abnormalities occur.

Atypical chronic myeloid leukemia is characterized by absence of Philadelphia chromosome, more advanced age of patients, lower levels of leukocytosis, a larger percentage of myeloblasts in the blood, lower count of thrombocytes and basophils in blood, lower amount of cells in the bone marrow, less significant inhibition of alkaline phosphatase in leukocytes, adverse prognosis and lower life expectancy compared to the classic CML.

Differential diagnosis of chronic myelogenous leukemia:

1. Primary myelofibrosis is a chronic, usually idiopathic disorder characterized by bone marrow fibrosis, splenomegaly, and anemia with nucleated and teardrop-shaped red blood cells (RBCs). Diagnosis requires bone marrow examination and exclusion of other conditions that can cause myelofibrosis.

2. Polycythemia vera is an idiopathic chronic myeloproliferative disorder characterized by an increase in RBC mass, which often manifests as an increased hematocrite (Hct). There is an increased risk of thrombosis and, rarely, acute leukemia and myelofibrotic transformation. Hepatosplenomegaly may also occur. Diagnosis is made by CBC, testing for *JAK2* mutations, and clinical criteria.
3. Essential thrombocytosis is characterized by an increased platelet count, megakaryocytic hyperplasia, and a hemorrhagic or thrombotic tendency. Symptoms and signs may include weakness, headaches, paresthesias, bleeding, splenomegaly, and erythromelalgia with digital ischemia. Diagnosis is based on a platelet count > 450,000/μL, normal RBC mass or normal Hct in the presence of adequate iron stores, and the absence of myelofibrosis, the Philadelphia chromosome (or *BCR-ABL* rearrangement), or any other disorder that could cause thrombocytosis.
4. Leukemoid reaction is marked granulocytic leukocytosis (ie, WBC > 30,000/μL) produced by normal bone marrow in response to systemic infection or cancer. Although not a neoplastic disorder, a leukemoid reaction with a very high WBC count may require testing to distinguish it from CML
5. Acute leukemia.

Treatment

- Tyrosine kinase inhibitor (TKI), sometimes accompanied with chemotherapy
- Stem cell transplantation

Except when stem cell transplantation is successful, treatment is not known to be curative. However, when tyrosine kinase inhibitors are used, survival is prolonged and maximum overall survival has not been reached. Some patients may be able to discontinue tryrosine kinase inhibitors and remain in remission. The durability of these remissions is as yet not known.
Imatinib and several newer drugs (*dasatinib, nilotinib*) inhibit the specific tyrosine kinase that results from the *BCR-ABL* gene product. Tyrosine kinase inhibitors (TKIs) are dramatically effective in achieving complete clinical and cytogenetic remissions of Ph chromosome–positive CML and are clearly superior to other regimens (eg, interferon with or without cytarabine). Imatinib also is superior to other treatments in the accelerated and blast phases. In the blast phase, combinations of chemotherapy with imatinib have a higher response rate than does therapy with either approach alone. Treatment tolerance is excellent. The high level of durable complete remissions associated with TKI therapy has led to the prospect of cure of the disease. However, the gene products of some *BCR-ABL* mutations are resistant to current TKIs and remain very difficult to control.
Older chemotherapy regimens are reserved for *BCR-ABL* –negative patients, patients who relapse after receiving a TKI, and patients in the blast phase. The main agents are busulfan, hydroxyurea, and interferon. *Hydroxyurea* is easiest to manage and has the fewest adverse effects. The starting dosage is generally 500 to 1000 mg per os twice daily. Blood counts should be done every 1 to 2 weeks and the dosage adjusted accordingly. *Busulfan* often causes unexpected general myelosuppression, and *interferon* causes a flu-like syndrome that frequently is unacceptable to patients. The main benefit of these therapies is reduction in distressing splenomegaly and adenopathy and control of the tumor burden to reduce the incidence of tumor lysis and gout. None of these therapies prolongs median survival > 1 year compared with untreated patients; thus, reduction in symptoms is the major goal, and therapy is not continued when patients have significant toxic symptoms.
Allogeneic stem cell transplantation can be useful for patients refractory to therapy. It is a curative modality in CML, associated with long-term survival rates of 40-60% when implemented in the chronic phase.
S*plenic radiation* is rarely used, however, it may be helpful in refractory cases of CML or in patients with terminal disease and marked splenomegaly. Total dosage usually ranges from 6 to

10 Gy delivered in fractions of 0.25 to 2 Gy/day. Treatment should begin with very low doses and with careful evaluation of the WBC count. Response is usually disappointing.
Splenectomy may alleviate abdominal discomfort, lessen thrombocytopenia, and relieve transfusion requirements when splenomegaly cannot be controlled with chemotherapy or irradiation. Splenectomy does not play a significant role during the chronic phase of CML.
Leukapheresis is rarely used in patients presenting with extreme leukocytosis and leukostatic complications. Single doses of high-dose cytarabine or high doses of hydroxyurea, with tumor lysis management, may be as effective and less cumbersome.

Prognosis depends on the clinical phase. With imatinib, survival is > 90% at 5 years after diagnosis for chronic phase CML. Prognosis is poor in the terminal phase. Ph chromosome–negative CML and chronic myelomonocytic leukemia have a worse prognosis than Ph chromosome–positive CML.

CHRONIC LYMPHOCYTIC LEUKEMIA.

Chronic lymphocytic leukemia (CLL) is a clonal hematopoietic stem cell disorder that involves mature-appearing defective neoplastic lymphocytes (almost always B cells) with an abnormally long life span.

Etiology. The etiologic factors for typical CLL are unknown, however, some cases appear to have a hereditary component.

Pathophysiology. In about 98% of cases, CD5+ B cells undergo malignant transformation, with lymphocytes initially accumulating in the bone marrow and then spreading to lymph nodes and other lymphoid tissues, eventually inducing splenomegaly and hepatomegaly. As CLL progresses, abnormal hematopoiesis results in anemia, neutropenia, thrombocytopenia, and decreased immunoglobulin production. Many patients develop hypogammaglobulinemia and impaired antibody response, perhaps related to increased T-suppressor cell activity. Patients have increased susceptibility to autoimmune disease characterized by immunohemolytic anemias (usually Coombs test–positive) or thrombocytopenia and a modest increase in risk of developing other cancers.
In 2 to 3% of cases, the clonal expansion is T cell in type, and even this group has a subtype (eg, large granular lymphocytes with cytopenias).
In addition, other chronic leukemic patterns have been categorized under CLL:

- Prolymphocytic leukemia
- Leukemic phase of cutaneous T-cell lymphoma (ie, Sézary syndrome)
- Hairy cell leukemia
- Lymphoma progressing to leukemia (ie, leukemic changes that occur in advanced stages of malignant lymphoma)

Differentiation of these subtypes from typical CLL is usually made by using light microscopy and phenotyping.

Clinical presentation.
The initial period. Complaints are often absent, sometimes fatigue, sweating, frequent colds are present. Objective data – moderate and painless enlargement of lymph nodes (the sequence of enlargement: neck, axillary, later - other groups).
Period of obvious clinical manifestations: complaints on the marked general weakness, decreased workability, nightsweats, weight loss, fever, enlargement of lymph nodes. Objective data – generalized enlargement of lymph nodes, non-specific skin lesions (cold sores, exfoliative erythroderma, urticaria, atopic dermatitis, fungal disease), enlargement of the spleen and liver. Leukemic infiltration can cause non-specific changes in the various organs and systems.
Terminal stage: an acute progressive deterioration of general condition of the patient,

accompanied by anemia, intoxication and exhaustion. It is characterized by the development of serious complications: generalized infection, renal failure, neuroleukemia, cardiomyopathy, respiratory failure, blast crisis.

Diagnosis.

- CBC and peripheral smear
- Bone marrow examination
- Immunophenotyping

CLL is confirmed by examining the peripheral smear and bone marrow; the hallmark is sustained, absolute peripheral lymphocytosis (> 5000/μL) and increased lymphocytes (> 30%) in the bone marrow. Differential diagnosis is simplified by immunophenotyping. Other findings at diagnosis may include hypogammaglobulinemia (< 15% of cases) and, rarely, elevated LDH. About 10% of patients present with moderate anemia (sometimes immunohemolytic), thrombocytopenia, or both. A monoclonal serum immunoglobulin spike of the same type may be found on the leukemic cell surface in 2 to 4% of cases.

Clinical staging is useful for prognosis and treatment. Two common approaches are Rai and Binet staging, primarily based on hematologic changes and extent of disease.

Rai

Stage 0 - Absolute lymphocytosis of > 10,000/μL in blood and ≥ 30% lymphocytes in bone marrow

Stage I - Stage 0 plus enlarged lymph nodes

Stage II - Stage 0 plus hepatomegaly or splenomegaly

Stage III - Stage 0 plus anemia with Hb < 11 g/dL

Stage IV - Stage 0 plus thrombocytopenia with platelet counts <100,000/μL

Binet

Stage A - Absolute lymphocytosis of > 10,000/μL in blood and ≥ 30% lymphocytes in bone marrow, Hb ≥ 10 g/dL, Platelets ≥100,000/μL, ≤ 2 involved sites*

Stage B - As for stage A, but 3–5 involved sites

Stage C - As for stage A or B, but Hb < 10 g/dL or platelets < 100,000/μL

* *Sites considered: Cervical, axillary, and inguinal lymph nodes; liver; and spleen.*

Differential diagnosis of CLL:

1. Lymphoma.
2. Lymphogranulomatosis.
3. Leukemoid reaction of lymphocytic type.
4. Acute leukemia.

Complications of CLL include blast crisis with the development of leukemic infiltration of inner organs and severe disorders of their function; the transformation into a malignant lymphoproliferative disease (acute leukemia, multiple myeloma, lymphosarcoma). The acute disorders of humoral immunity lead to severe infectious complications.

Treatment.

1. **Specific therapy** includes
   - Chemotherapy
   - Corticosteroids
   - Monoclonal antibody therapy
   - Radiation therapy

These modalities may alleviate symptoms and prolong survival. Overtreatment is more dangerous than undertreatment.

Patients whose presentation is typical B-cell CLL with no manifestations of the disease other than bone marrow involvement and Iymphocytosis (i.e., Rai stage 0 and Binet stage A) can be followed without specific therapy for their malignancy. These patients have a median survival > 10 years, and some will never require therapy for this disorder.

If the patient has an adequate number of circulating normal blood cells and is asymptomatic, many physicians would not initiate therapy for patients in the intermediate stage of the disease manifested by lymphadenopathy and/or hepatosplenomegaly. However, the median survival for these patients is 7 years, and most will require treatment in the first few years of follow-up.

Patients who present with bone marrow failure (i.e., Rai stage III or IV or Binet stage C) will require initial therapy in almost all cases. These patients have a serious disorder with a median survival of only 1.5 years.

Corticosteroids Immunohemolytic anemia and thrombocytopenia are indications for corticosteroids. Prednisone 1 mg/kg per os once/day may occasionally result in striking, rapid improvement in patients with advanced CLL, although response is often brief. The metabolic complications and increasing rate and severity of infections warrant caution in its prolonged use.

Immune manifestations of typical B-cell CLL should be managed independently of specific antileukemia therapy. For example, glucocorticoid therapy for autoimmune cytopenias and γ-globulin replacement for patients with hypogammaglobulinemia, repeated or refractory infections should be used whether or not antileukemia therapy is given.

Chemotherapy. The most common treatments for patients with typical B-cell CLL have been chlorambucil or fludarabine, alone or in combination. Chlorambucil can be administered orally with few immediate side effects, while fludarabine is administered IV and is associated with significant immune suppression. However, fludarabine is by far the more active agent and is the only drug associated with a significant incidence of complete remission. The following combinations help to achieve complete responses in 69% of patients (and those responses are associated with molecular remissions in half of the cases):

- fludarabine (25 mg/m^2 days 2-4 on cycle 1 and days 1-3 in subsequent cycles) with rituximab (375-500 mg/m^2 day 1)
- fludarabine with rituximab and cyclophosphamide (250 mg/m^2 days 1-3)

Monoclonal antibody therapy. Rituximab is the first monoclonal antibody used in the successful treatment of lymphoid cancers. In previously untreated patients, the response rate is 75%, with 20% of patients achieving complete remission. Alemtuzumab has a 33% response rate in previously treated patients refractory to fludarabine and a 75 to 80% response rate in previously untreated patients. More problems with immunosuppression occur with alemtuzumab than with rituximab. Rituximab has been combined with fludarabine and with fludarabine and cyclophosphamide; these combinations have markedly improved the complete remission rate in both previously treated and untreated patients. Alemtuzumab is now being combined with rituximab and with chemotherapy to treat minimal residual disease and has effectively cleared bone marrow infiltration. Reactivation of cytomegalovirus and other opportunistic infections has occurred with alemtuzumab. Reactivation of hepatitis B infection may occur with rituximab.

Obinutuzumab is a newer monoclonal antibody that targets the same CLL cell surface protein as rituximab. The combination of obinutuzumab and chlorambucil was recently found to be superior to rituximab in prolonging progression-free survival and achieving a complete response to treatment.

In general, monoclonal antibodies are well tolerated, although they may cause allergic reactions and significant immunosuppression. This favorable toxicity profile allows these agents to be combined with conventional chemotherapy, often with excellent clinical efficacy.

Radiation therapy. Local irradiation for palliation may be given to areas of lymphadenopathy or for liver and spleen involvement that does not respond to chemotherapy. Total body irradiation in small doses is occasionally successful in temporarily ameliorating symptoms.

2. **Supportive care** includes
   - Transfusion of packed RBCs or erythropoietin injections for anemia
   - Platelet transfusions for bleeding associated with thrombocytopenia
   - Antimicrobials for bacterial, fungal, or viral infections. Because neutropenia and agammaglobulinemia limit bacterial killing, antibiotic therapy should be bactericidal.

3. Young patients with this disease can be candidates for **bone marrow transplantation**. Allogeneic bone marrow transplantation can be curative but is associated with a significant treatment-related mortality rate.

Prognosis: The median survival of patients with B-cell CLL or its complications is about 7 to 10 years. Patients in Rai stage 0 to II at diagnosis may survive for 5 to 20 years without treatment. Patients in Rai stage III or IV are more likely to die within 3 to 4 years of diagnosis. Progression to bone marrow failure is usually associated with short survival. Patients with CLL are more likely to develop a secondary cancer, especially skin cancer.

Control of initial level of knowledge

1. What is the average lifespan of granulocytes?
   A. 1 to 3 hours.
   B. from 12 hours to 10 days.
   C. from 100 to 130 days.
   D. 6 months to 1 year.
   E. from 1 year to 3 years.

2. What belongs to the central organs of hematopoiesis?
   A. bone marrow and lymph nodes.
   B. brain and spinal cord.
   C. bone marrow and thymus.
   D. spleen and liver.
   E. spleen and lymph nodes.

3. Which organ is responsible for the maturation and proliferation of T lymphocytes?
   A. thymus.
   B. yellow bone marrow.
   C. red bone marrow.
   D. spleen.
   E. liver.

4. Which organ is responsible for the maturation and proliferation of B lymphocytes?
   A. thymus.
   B. yellow bone marrow.
   C. red bone marrow.
   D. spleen.
   E. liver.

5. Which cells belong to agranulocytes?
   A. lymphocytes, monocytes.
   B. reticulocytes, red blood cells.
   C. megakaryocytes, platelets.

D. neutrophils, eosinophils, basophils.
E. fibroblasts, osteoblasts.

6. Which cells belong to granulocytes?
   A. lymphocytes, monocytes.
   B. reticulocytes, red blood cells.
   C. megakaryocytes, platelets.
   D. neutrophils, eosinophils, basophils.
   E. fibroblasts, osteoblasts.

7. What is the main function of B-lymphocytes?
   A. hemostatic.
   B. transport of oxygen.
   C. synthesis of cytokines.
   D. phagocytic.
   E. antibody synthesis.

8. What is the main function of granulocytes?
   A. hemostatic.
   B. transport of oxygen.
   C. synthesis of cytokines.
   D. phagocytic.
   E. antibody synthesis.

9. What bone marrow cells are called blasts?
   A. pluripotent stem cells.
   B. colony forming units, able to differentiate in several ways.
   C. differentiated mature cells.
   D. maturing cells that already have morphological differences.
   E. immature cells that have no morphological differences, but they can be differentiated in one direction.

10. What regulatory substances are synthesized by cells of the hematopoietic microenvironment?
    A. steroids
    B. colony stimulating factor.
    B. acetylcholine.
    G. hemocoagulation factors.
    D. vitamins.

Correct answers on "Chronic leukemia" topic (initial level of knowledge)

1. B	6. D
2. C	7. E
3. A	8. D
4. C	9. E
5. A	10. B

Control of initial level of knowledge

1. Diagnostic criterion for CML is:
A. leukocytosis.
B. myeloid hyperplasia with the presence of the Philadelphia chromosome.
C. eosinophilic-basophilic association.
D. anemia.
E. 60% promyeloblasts in myelogram.

2. Philadelphia chromosome is:
A. translocation t (9; 16).
B. translocation t (9; 22).
C. translocation t (9; 28).
D. trisomy for the X-chromosome.
E. mutation in the tyrosine kinase gene.

3. Eosinophilic-basophilic association is:
A. Reduction of eosinophil and basophil count in the peripheral blood.
B. Increase of eosinophils and reduction of basophils in the peripheral blood.
C. Reduction of eosinophils and increase of basophils in the peripheral blood.
D. The increase of eosinophils and basophils in the peripheral blood.
E. Absence of eosinophils and basophils in the peripheral blood.

4. What differs blast crisis in CML from acute myeloid leukemia:
A. absence of blasts in the peripheral blood.
B. absence of eosinophilic-basophilic association.
C. absence of leukemic gap.
D. absence of anemia.
E. absence of thrombocytopenia.

5. What causes intoxication syndrome in leukemia?
A. intradermal hemorrhages.
B. enlargement of the liver and spleen.
C. development of renal failure.
D. reduction of red blood cells.
E. increased degradation of leukemic cells.

6. What is an indication for splenectomy in case of CLL:
A. if splenomegaly decreases when exposed to radiation and cytostatic therapy.
B. if splenomegaly causes obvious abdominal discomfort.
C. presence of aplastic anemia and thrombocytopenia.
D. preparation for stem cell transplantation.

7. What cells represent the morphological substrate of tumor in chronic myeloid leukemia?
A. erythrocytes.
B. granulocytes.
C. monocytes.
D. lymphocytes.
E. platelets.

8. A characteristic hematological feature of CLL:
A. Gumprecht shadows.
B. Liebman spots.
C. Charcot-Leyden crystals.
D. Erb point.
E. Lyon sign.

9. What is the indication for radiotherapy at leucosis?
A. extramedullary tumor formation.
B. CNS involvement.
C. infectious and inflammatory complications.
D. anemia.
E. hyperthermia.

10. The number of what cells increases in chronic lymphocytic leukemia?
A. platelets.
B. granulocytes.
C. monocytes.
D. erythrocytes.
E. lymphocytes.

Correct answers on "Chronic leukemia" topic (final level of knowledge)

1. B	6. B
2. B	7. B
3. D	8. A
4. C	9. A
5. E	10. E

Case-based questions.

№1

Patient, 27 years old, complains on fatigue, sweating, dull pain in the left upper quadrant, especially after meals. The mentioned above complaints exist about 1 year. Objective data: enlargement of the spleen and liver. CBC: erythrocytes - 3,2 × 10^{12} / l, hemoglobin - 100 g / l, CI- 0.87, leukocytes - 112 × 10^{9} / L, blasts - 7%, eosinophils - 5%, myelocytes - 15%, young granulocytes - 16%, bands - 10%, segmented - 45%, lymphocytes - 2%, monocytes - 0%, reticulocytes - 0.3%, platelets - 420 × 10^{9} / l, ESR- 25 mm / h. What is the most likely diagnosis?
A. Polycythemia vera
B. Liver cirrhosis
C. Chronic lymphocytic leukemia
D. Acute leukemia
E. Chronic myeloid leukemia

№2

The patient, 50 years old, complains of mild fatigue, loss of appetite, night sweats, abdominal discomfort, weight loss. Objective data: pale skin, hepatosplenomegaly, in peripheral blood - a significant leukocytosis with leukocyte shift to the left, basophilic-eosinophilic association, anemia, thrombocytopenia. Which of the following data could confirm the preliminary diagnosis of chronic myeloid leukemia?
A. The presence of the Philadelphia chromosome
B. Gumprecht shadows
B. Elevated levels of alkaline phosphatase
G. Reduced level of cyanocobalamin
D. Total bone marrow hypoplasia with megakariocytosis

№3

Woman, 52 years old, complains on weakness, sweating, and increased cervical lymph nodes within a month. Medical history - frequent "colds". Body temperature - 37,5°C. Two cervical lymph nodes of tight elastic consistency are palpable on the right side of the neck 1 × 2 cm and 1 × 1,5 cm, not painful on palpation, not connected to each other and to the surrounding tissues. CBC: leukocytosis 34 × 10^{9} / L, lymphocytes make up 68%, prolymphocytes - 6%. ESR - 19 mm / h. Gumprecht cells are found. Myelogram - 38% of lymphocytes. Which of the following is the most likely diagnosis?
A. Chronic lymphocytic leukemia
B. Lymphoma
C. Regional lymphadenitis
D. Acute lymphocytic leukemia
E. Lymphogranulomatosis

№4

Patient, 56 years old, noticed an increase in cervical lymph nodes, general weakness, shortness of breath on exertion, cough. Objective data: enlargement of cervical and axillary lymph nodes, liver and spleen. Blood pressure - 140/80 mm Hg. CBC: red blood cells - 2,5 × 10^{12} / l; hemoglobin - 106 g / l; leukocytes - 77 × 10^{9} / L; eosinophil - 1%; stab - 2%; segmented - 19%; lymphocytes - 78%; ESR - 40 mm / h. What is the most likely diagnosis in this case?
A. Acute lymphocytic leukemia
B. Chronic lymphocytic leukemia
C. Pulmonary tuberculosis
D. Infectious mononucleosis
E. Lung cancer

№5

Patient, 49 years old, complains on general weakness, dizziness, headaches, burning pain in the extremities, and the left upper abdominal discomfort. His condition deteriorated about 2 months ago. Objective data: facial skin is red, redness of the sclera, enlarged liver and spleen, heart rate 92 / min., blood pressure - 166/100 mm Hg. CBC: hemoglobin 210 g / l, erythrocytes - 6.9×10^{12} / L, white blood cells - 13 × 10 / L, platelets - 960×10^{9} / L. What is the most likely diagnosis in this case?

A. Chronic myeloid leukemia.
B. Idiopathic myelofibrosis.
C. Aplastic anemia.
D. Essential thrombocytosis.
E. Polycythemia vera.

№6

The patient, 22 years old, complains on fatigue during exercise, however the general condition is good. Objective examination revealed a slight increase of peripheral lymph nodes. After in-depth clinical and laboratory examination a chronic lymphocytic leukemia was diagnosed. Determine the optimal management of a patient:

A. Radiation therapy
B. Monotherapy with cytostatic drug
C. Polychemotherapy
D. Dynamic observation
E. Stem cell transplantation

№7

The patient, 67, suffers from chronic myelogenous leukemia. At the time of the examination complains on general weakness, feeling of heaviness in the left upper quadrant of abdomen. Objective data: pulse - 78 / min., blood pressure - 150/90 mm Hg., body temperature 37˚C, the lower part of the spleen is palpable. CBC: red blood cells - $3{,}3 \times 10^{12}$ / l, hemoglobin - 104 g / l, color index - 0.94, leukocytes 63×10^{9} / L, eosinophils - 6%, basophils - 5%, bands - 8%, segmented - 71%, lymphocytes - 18% monocytes - 2%, platelets - 448×10^{9} / l, ESR - 16 mm/h. What preparation should be used for monotherapy?

A. Vincristine.
B. Fludarabine.
C. Imatinib.
D. Prednisolone.
E. Cyclophosphamide.

№8

The patient, 44 years old, suffers from chronic lymphocytic leukemia. He complains on considerable general weakness, shortness of breath, pain in the left upper quadrant of abdomen. Objective data: jaundice of skin and mucous membranes, pulse - 108 / min., AT - 90/60, generalized enlargement of lymph nodes, significant enlargement of spleen. CBC: red blood cells - $2{,}5 \times 10^{12}$ / l, hemoglobin - 86 g / l, color index - 1.03, eosinophils - 1%, bands - 1%, segmented - 26%, lymphocytes - 69%, monocytes - 3 %, platelets 106×10^{9} / l, ESR - 28 mm / h. Total bilirubin - 65 mmol / l. Coombs test is positive. What preparation should be assigned in a complex treatment to reduce signs of autoimmune anemia and splenomegaly?

A. Vitamin B12
B. Prednisolone
C. Folate
D. α2-interferon
E. Tardyferon

№9

The patient, 59, suffers from chronic myelogenous leukemia. During the last week the general condition of the patient deteriorated. There were complaints about significant general weakness, shortness of breath on minimal exertion, headache, pain in the back and joints. Objective data: skin pallor, pulse - 112 / min., BP - 90/50 mm Hg., body temperature 39,2˚C, hepatosplenomegaly. CBC: red blood cells - $2,2 \times 10^{12}$ / l, hemoglobin - 69 g / l, color index - 0.94, leukocytes - 198×10^{9} / L blasts - 38%, eosinophils - 4%, basophils - 9%, bands - 0%, segmented - 37%, lymphocytes - 11% monocytes - 1%, platelets - 127×10^{9} / l, ESR - 49 mm / h. What therapeutic strategy should be applied in this case?

A. Radiation therapy
B. Monotherapy with cytostatic drug
C. Polychemotherapy
D. Dynamic observation
E. Stem cell transplantation

№10

The patient is 55 years old, his diagnosis is chronic myelogenous leukemia. For a long time he has been feeling quite well because of cytostatic therapy. 5 days ago a pain in the left upper quadrant has developed, radiating to the back, worsening at deep breathing. According to the ultrasonography data, the spleen is enlarged, there are signs of spleen infarction. What is the best method to treat this complication?

A. Plasmapheresis
B. Treatment with glucocorticoids
C. Polychemotherapy
D. Radiation of the spleen
E. Splenectomy

Correct answers on "Chronic leukemia" (case-based questions)

1. E	5. E	9. C
2. A	6. D	10. E
3. A	7. C	
4. B	8. B	

Control questions.

1. Definition of leukemia.
2. Definition of chronic myelogenous leukemia.
3. Describe the etiology and pathogenesis of chronic myelogenous leukemia.
4. Describe the clinical manifestations of chronic myelogenous leukemia at different stages of the disease.
5. The results of laboratory data and instrumental studies in chronic myelogenous leukemia.
6. Identify the clinical features of atypical variant of chronic myelogenous leukemia.
7. Differential diagnosis of chronic myelogenous leukemia.
8. Identify chronic myelogenous leukemia treatment program.
9. Prevention and prognosis of chronic myelogenous leukemia.
10. Definition chronic lymphocytic leukemia.
11. Describe the etiology and pathogenesis of chronic lymphocytic leukemia.
12. Describe the clinical manifestations of chronic lymphocytic leukemia at different stages of the disease.
13. The results of laboratory data and instrumental studies in chronic lymphocytic leukemia.
14. Identify the features of different clinical variants of chronic lymphocytic leukemia.
15. Differential diagnosis of chronic lymphocytic leukemia.
16. Determine the program of treatment of chronic lymphocytic leukemia.
17. Prevention and prognosis of chronic lymphocytic leukemia.

Further reading:

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2. Chisholm-Burns M.A., Wells B.G., Schwinghammer T.L. et al. Pharmacotherapy principles & practice. - The McGraw-Hill Companies, Inc., 2008. – 1671 p.
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4. Longo D. Harrison's Hematology and oncology. - The McGraw-Hill Education / Medical; 2 edition (April 29, 2013). – 848 p.
5. Merck Manual Professional Version, available at: http://www.merckmanuals.com/professional/hematology-and-oncology/leukemias/chronic-lymphocytic-leukemia-cll, assessed Aug, 21 2016.
6. European LeukemiaNet recommendations for the management of chronic myeloid leukemia, 2013.
7. Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2012.
8. NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia. Version 2.2014.
9. Guidelines on the diagnosis, investigation and management of Chronic Lymphocytic Leukaemia, British Committee for Standards in Haematology, 2011
10. Chisholm-Burns M.A., Wells B.G., Schwinghammer T.L. et al. Pharmacotherapy principles & practice. - The McGraw-Hill Companies, Inc., 2008. – 1671 p.