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Факультет VI по підготовці іноземних студентів

ЗАТВЕРДЖЕНО
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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

Гострі лейкози

Харків 2016

«Acute 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 peak incidence of acute lymphocytic leukemia is at age 2-5 years. In adults, the disease is found only in 20% of patients. Acute lymphocytic leukemia is the most common malignant tumor in pediatric patients and composes 1/3 of all cancers in children. In case of acute lymphocytic leukemia 5-year survival in childhood is 80%, in adults - 40%. A second rise in incidence occurs after age 45.

The average age of patients with acute myeloid leukemia is 50 years. The incidence of acute myeloid leukemia has increased from 1.8 cases per 100,000 of population in childhood to 17.7 per 100,000 of population over the age of 65 years. In acute myeloid leukemia 5-year survival in patients younger than 20 years was 50%, in patients older than 60 years - less than 20%.

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 acute leukemia;
- to acquaint students with the etiology and pathogenesis of different types of acute leukemia;
- to acquaint students with the modern classification of acute leukemia;
- to teach students to recognize the major symptoms and syndromes in acute leukemia;
- to acquaint students with the research methods used for the diagnosis of acute 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 acute leukemia;
- to teach students to prescribe treatment for acute leukemia.

What should a student know?

- main etiological factors and pathogenetic mechanisms of acute leukemia;
- main clinical syndromes of acute leukemia;
- complaints and physical examination data in acute leukemia;
- methods of physical examination of patients with acute leukemia;
- diagnostic value of complete blood count and myelogram in acute 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 acute leukemia;
- management of patients with acute leukemia;
- treatment of acute 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 acute leukemia;
- to set inspection program for patient with acute leukemia;
- to interpret the results of laboratory tests;
- to perform differential diagnosis of acute leukemia;
- to prescribe treatment for patients with acute 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.

Acute leukemia occurs when a hematopoietic stem cell undergoes malignant transformation into a primitive, undifferentiated cell with abnormal longevity (mainly blasts).

Etiology

- Exposure to ionizing radiation (nuclear disasters, radiation therapy) or to chemicals (eg, benzene)

- Prior treatment with certain antineoplastic drugs, particularly procarbazine, nitrosureas (cyclophosphamide, melphalan), and epipodophyllotoxins (etoposide, teniposide)
- Infection with a virus (human T-lymphotropic virus 1 and 2, Epstein-Barr virus, human herpesvirus 8)
- Chromosomal translocations
- Preexisting conditions, including immunodeficiency disorders, chronic myeloproliferative disorders, and chromosomal disorders (Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, Down syndrome, infantile X-linked agammaglobulinemia)

Pathophysiology

Malignant transformation usually occurs at the pluripotent stem cell level. Abnormal proliferation, clonal expansion, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells. Manifestations of leukemia are due to suppression of normal blood cell formation and organ infiltration by leukemic cells. Inhibitory factors produced by leukemic cells and replacement of marrow space may suppress normal hematopoiesis, with ensuing anemia, thrombocytopenia, and granulocytopenia. Organ infiltration results in enlargement of the liver, spleen, and lymph nodes, and occasionally, in kidney and gonadal involvement. Meningeal infiltration results in clinical features associated with increasing intracranial pressure.

Classification

Acute leukemias are divided into lymphocytic (ALL) and myelogenous (AML) types, which may be further subdivided by the French-American-British (FAB) classification:

ALL

L1 - Lymphoblasts with uniform, round nuclei and scant cytoplasm
L2 - More variability of lymphoblasts, sometimes irregular nuclei with more cytoplasm than L1
L3 - Lymphoblasts with finer nuclear chromatin and blue to deep blue cytoplasm that contains vacuoles

AML

M1 - Undifferentiated myeloblastic. No cytoplasmic granulation
M2 - Differentiated myeloblastic. Sparse granulation in few to many cells
M3 – Promyelocytic. Granulation typical of promyelocytic morphology
M4 – Myelomonoblastic. Mixed myeloblastic and monocytoid morphology
M5 – Monoblastic. Pure monoblastic morphology
M6 – Erythroleukemic. Predominantly immature erythroblastic morphology, sometimes megaloblastic appearance
M7 – Megakaryoblastic. Cells with shaggy borders that may show some budding

Symptoms and Signs

Symptoms may be present for only days to weeks before diagnosis. Disrupted hematopoiesis leads to the most common presenting symptoms (anemia, infection, easy bruising and bleeding). Other presenting symptoms and signs are usually nonspecific (eg, pallor, fatigue, fever, malaise, weight loss, tachycardia, chest pain) and are attributable to anemia and a hypermetabolic state. The cause of fever often is not found, although granulocytopenia may lead to a rapidly progressing and potentially life-threatening bacterial infection. Bleeding is usually manifested by petechiae, easy bruising, epistaxis, bleeding gums, or menstrual irregularity. Hematuria and GI bleeding are uncommon. Bone marrow and periosteal infiltration may cause bone and joint pain, especially in children with ALL. Initial CNS involvement or leukemic meningitis (manifesting as headaches, vomiting, irritability, cranial nerve palsies, seizures, and papilledema) is uncommon. Extramedullary infiltration by leukemic cells may cause lymphadenopathy, splenomegaly,

hepatomegaly, and leukemia cutis (a raised, nonpruritic rash). Gum hyperplasia may be prominent, particularly in AML.

Clinical peculiarities of ALL:
- More often found in children than in adults;
- Moderately progressive course of the disease;
- Leukemia cutis is a typical clinical symptom;
- Enlargement of lymph nodes;
- Often develops neuroleukemia;
- Leukemic infiltration of testicles;
- Greater frequency of pain in bones;
- Hyperthermia syndrome is very typical;
- The efficacy of cytostatic therapy is higher than in other leukemias.

Clinical peculiarities of AML
- More often found in adults;
- Rapidly progressive disease;
- Ulcerative and necrotic lesions of skin and mucous membranes are found very often;
- Greater severity of hemorrhagic syndrome.

Diagnosis:
CBC and peripheral smear are the first tests done; pancytopenia and peripheral blasts suggest acute leukemia. Blast cells in the peripheral smear may approach 90% of WBC count.
Bone marrow examination (aspiration or needle biopsy) is routinely done, although the diagnosis can usually be made from the peripheral smear. Blast cells in the bone marrow are classically between 25 and 95%. Aplastic anemia, viral infections such as infectious mononucleosis, and vitamin B_{12} and folate deficiency should be considered in the differential diagnosis of severe pancytopenia. Leukemoid reactions to infectious disease (such as TB) can rarely manifest with high blast counts.
Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies help distinguish the blasts of ALL from those of AML or other disease processes. Specific B-cell, T-cell, and myeloid-antigen monoclonal antibodies, together with flow cytometry, are essential in classifying the acute leukemias, which is critical for treatment.
Other laboratory findings may include hyperuricemia, hyperphosphatemia, hyperkalemia or hypokalemia, hypocalcemia, elevated serum hepatic transaminases or LDH, hypoglycemia, and hypoxia.
CT of the head is done in patients with CNS symptoms. Chest x-ray should be done to detect mediastinal masses, especially before the patient is given anesthesia. CT, MRI, or abdominal ultrasonography may help assess splenomegaly or leukemic infiltration of other organs.

Differential diagnosis of acute leukemia.
1. Leukemoid reaction.
2. Hypoplastic anemia.
3. Agranulocytosis.
4. Megaloblastic anemia (dif. diagnosis with acute erythromyelosis).
5. Metastases of malignant tumors in the bone marrow.

Complications of acute leukemia.
The complications of acute leukemia, which represent a direct threat to life are: tumor metastasis (with the development of organ failure), heavy bleeding, severe infections.

Treatment is based on two principal strategies:

- Chemotherapy
- Supportive care

The goal of treatment is complete remission, including resolution of abnormal clinical features, restoration of normal blood counts and normal hematopoiesis with < 5% blast cells in the bone marrow, and elimination of the leukemic clone. Although basic principles in treating ALL and AML are similar, the drug regimens differ. The complex nature of patients' clinical situations and the available treatment protocols necessitate an experienced team. Whenever possible, patients should be treated at specialized medical centers, particularly during critical phases (remission induction).

Chemotherapy for ALL includes 4 general phases:

1. *Induction therapy*

The goal is to induce remission. Several regimens emphasize early introduction of an intensive multidrug regimen. Remission can be induced with daily oral prednisone (60 mg/m^2) and weekly IV vincristine (0,1% 1 ml) 2 ml per injection with the addition of an anthracycline or asparaginase (10000 IU) 6000 IU/m^2 per os daily. Other drugs and combinations that may be introduced early in treatment are cytarabine and etoposide as well as cyclophosphamide. In some regimens, intermediate-dose or high-dose IV methotrexate is given with leucovorin rescue. The combinations and their dosages are modified according to the presence of risk factors. Imatinib can be added to the drug regimen in patients with Ph chromosome–positive ALL.

2. *CNS prophylaxis*

An important site of leukemic infiltration is the meninges; prophylaxis and treatment may include intrathecal methotrexate 12,5 mg\m^2 4-6 times with 3-5 days interval, cytarabine, and corticosteroids in combination or methotrexate and cytarabine singly. Cranial nerve or whole-brain irradiation may be necessary and is often used for patients at high risk of CNS disease (eg, high WBC count, high serum LDH, B-cell phenotype), but its use has been decreasing in recent years.

3. *Consolidation therapy*

The goal of consolidation is to prevent leukemic regrowth. Consolidation therapy usually lasts a few months and combines drugs that have different mechanisms of action than drugs used in induction regimens. Allogeneic stem cell transplantation is recommended as consolidation therapy for Ph chromosome–positive ALL in adults or for second or later relapses or remissions.

4. *Maintenance therapy*

Most regimens include maintenance therapy with methotrexate (20 mg/m^2 once per week) and mercaptopurine (60 mg/m^2 per os daily). Therapy duration is usually 2½ to 3 years but may be shorter when regimens that are more intensive in earlier phases are used. Clinical testing of monoclonal antibodies directed against proteins on the leukemic cell surface are underway, with some new agents showing promise.

Therapy is usually short and intensive for Burkitt leukemia or ALL with mature B-cells (FAB L3 morphology). For patients in continuous complete remission for 1 year after therapy stops, the risk of relapse is small.

Relapse

Leukemic cells may reappear in the bone marrow, the CNS, the testes, or other sites. Bone marrow relapse is particularly ominous. Although a new round of chemotherapy may induce a 2nd remission in 80 to 90% of children (30 to 40% of adults), subsequent remissions tend to be brief. Chemotherapy causes only a few patients with early bone marrow relapse to achieve long disease-free 2nd remissions or cure.

If an HLA-matched sibling is available, stem cell transplantation offers the greatest hope of long-term remission or cure. Cells from other relatives or from matched, unrelated donors are sometimes used. Transplantation is rarely used for patients > 65 yr because it is much less likely to be successful and because adverse effects are much more likely to be fatal.

When relapse involves the CNS, treatment includes intrathecal methotrexate (with or without cytarabine or corticosteroids) twice weekly until all signs disappear. Most regimens include systemic reinduction chemotherapy because of the likelihood of systemic spread of blast cells. The role of continued intrathecal drug use or CNS irradiation is unclear.
Testicular relapse may be evidenced clinically by painless firm swelling of a testis or may be identified on biopsy. If unilateral testicular involvement is clinically evident, the apparently uninvolved testis should undergo biopsy. Treatment is radiation therapy of the involved testis and administration of systemic reinduction therapy as for isolated CNS relapse.

Chemotherapy for AML includes 2 general phases:

1. Induction therapy

Initial therapy attempts to induce remission and differs most from ALL in that AML responds to fewer drugs. The basic induction regimen includes cytarabine by continuous IV infusion (100 mg/m^2) or high doses for 5 to 7 days; daunorubicin (60-90 mg/m^2) or idarubicin (12 mg/m^2) is given IV for 3 days during this time. Some regimens include 6-thioguanine, etoposide, vincristine, and prednisone, but their contribution is unclear. Treatment usually results in significant myelosuppression, with infection or bleeding. There is significant latency before marrow recovery. During this time, meticulous preventive and supportive care is vital.
In APL and some other cases of AML, disseminated intravascular coagulation (DIC) may be present when leukemia is diagnosed and may worsen as leukemic cell lysis releases procoagulant. In APL with the translocation t(15;17), all- *trans* retinoic acid (tretinoin) corrects the DIC in 2 to 5 days; combined with daunorubicin or idarubicin, this regimen can induce remission in 80 to 90% of patients and bring about long-term survival in 65 to 70%. Arsenic trioxide is also very active in APL.

2. Consolidation therapy

After remission, many regimens involve a phase of intensification with the same drugs used for induction or with other drugs. High-dose cytarabine regimens may lengthen remission duration, particularly when given for consolidation in patients < 60 yr. CNS prophylaxis usually is not given to adult patients because with better systemic disease control, CNS leukemia is a less frequent complication. In AML patients who have completed consolidation, maintenance therapy has no demonstrated role.

Relapse

Patients who have not responded to treatment and younger patients who are in remission but who are at high risk of relapse (generally identified by high-risk molecular or chromosomal abnormalities) may be given high-dose chemotherapy and stem cell transplantation. Extramedullary sites are infrequently involved in isolated relapse. When relapse occurs, additional chemotherapy for patients unable to undergo stem cell transplantation is less effective and often poorly tolerated. Another course of chemotherapy is most effective in younger patients and in patients whose initial remission lasted > 1 yr.

Supportive care

Supportive care is similar in the acute leukemias and may include:

- Transfusions
- Antibiotics or antifungal drugs
- Hydration and urine alkalinization
- Psychologic support

Transfusions of platelets, RBCs, and granulocytes are administered as needed to patients with bleeding, anemia, and neutropenia, respectively. Prophylactic platelet transfusion is done when platelets fall to <10,000/μL; a higher threshold (20,000/μL) is used for patients with the triad of fever, disseminated intravascular coagulation, and mucositis secondary to chemotherapy. Anemia (Hb < 8 g/dL) is treated with transfusions of packed RBCs. Granulocyte transfusions

may help neutropenic patients with gram-negative or other serious infections but have no proven benefit as prophylaxis.

Antimicrobials are often needed because patients are neutropenic and immunosuppressed; in such patients, infections can progress quickly with little clinical prodrome. After appropriate studies and cultures have been done, febrile patients with neutrophil counts < 500/μL should begin treatment with a broad-spectrum bactericidal antibiotic that is effective against gram-positive and gram-negative organisms (eg, ceftazidime, imipenem, cilastatin). Fungal infections, especially pneumonias, are becoming more common; these are difficult to diagnose, so chest CT should be done early (ie, < 72 h, depending on degree of suspicion) to detect fungal pneumonia. Empiric antifungal therapy should be given if antibacterial therapy is not effective within 72 h. In patients with refractory pneumonitis, *Pneumocystis jirovecii* infection or a viral infection should be suspected and confirmed by bronchoscopy and bronchoalveolar lavage and treated appropriately. Empiric therapy with trimethoprim/sulfamethoxazole (TMP/SMX), amphotericin B, and acyclovir or other analogs, often with granulocyte transfusions, is often necessary. In patients with drug-induced immunosuppression at risk of opportunistic infections, TMP/SMX is given to prevent *P. jirovecii* pneumonia.

Hydration (twice the daily maintenance volume), urine alkalinization (pH 7 to 8), and electrolyte monitoring can prevent the hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia (tumor lysis syndrome) caused by the rapid lysis of leukemic cells during initial therapy (particularly in ALL). Hyperuricemia can be minimized by reducing the conversion of xanthine to uric acid by giving allopurinol (a xanthine oxidase inhibitor) or rasburicase (a recombinant urate-oxidase enzyme) before starting chemotherapy.

Psychologic support may help patients and their families weather the shock of illness and the rigors of treatment for a potentially life-threatening condition.

Prognosis

Cure is a realistic goal for both ALL and AML, especially in younger patients. Prognosis is worse in infants and the elderly and in those with hepatic or renal dysfunction, CNS involvement, testicular involvement, myelodysplasia, or a high WBC count (>25,000/μL). Survival in untreated acute leukemia generally is 3 to 6 months. Prognosis varies according to multiple variables including patient age, karyotype, response to therapy, and performance status.

In case of **ALL** *the favorable prognostic factors* include:

- Age 3 to 9 years
- WBC count <25,000/μL (< 50,000/μL in children)
- French-American-British (FAB) L1 morphology
- Leukemic cell karyotype with > 50 chromosomes and t(12;21)
- No CNS disease at diagnosis

Unfavorable factors include the following:

- A leukemic cell karyotype with chromosomes that are normal in number but abnormal in morphology (pseudodiploid)
- Presence of the Philadelphia (Ph) chromosome t(9;22)
- Increased age in adults
- B-cell immunophenotype with surface or cytoplasmic immunoglobulin
- Early precursor T-cell phenotype; BCR-ABL–like molecular signature

Regardless of prognostic factors, the likelihood of initial remission is ≥ 95% in children and 70 to 90% in adults. Of children, 75% or more have continuous disease-free survival for 5 years and appear cured. Of adults, 30 to 40% have continuous disease-free survival for 5 years. Imatinib improves outcome in adults and children with Ph chromosome–positive ALL. Most investigatory

protocols select patients with poor prognostic factors for more intense therapy, because the increased risk of and toxicity from treatment are outweighed by the greater risk of treatment failure leading to death.

In case of **AML**, remission induction rates range from 50 to 85%. Long-term disease-free survival occurs in 20 to 40% of patients and increases to 40 to 50% in younger patients treated with intensive chemotherapy or stem cell transplantation.
Prognostic factors help determine treatment protocol and intensity; patients with strongly negative prognostic features are usually given more intense forms of therapy because the potential benefits are thought to justify the increased treatment toxicity. An important prognostic factor is the leukemia cell karyotype. The specific chromosomal rearrangements of the different forms of AML affect the outcome. Three clinical groups have been identified: favorable, intermediate, and poor. Patients who have the cytogenetic findings of t(8;21), t(15;17), and inv(16) typically have a favorable response to therapy, durable remission, and improved survival. Patients with a normal karyotype have an intermediate prognosis, and patients with a poor prognosis are those with a deletion of chromosome 5 or 7, trisomy 8, or a karyotype with > 3 abnormalities. Molecular genetic abnormalities are becoming more important in refining prognosis and therapy in AML. Mutations in Flt3 kinase in particular indicate a poorer prognosis and are targets for additional therapy. Other negative factors include increasing age, a preceding myelodysplastic phase, secondary leukemia, high WBC count, and absence of Auer rods.

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 "Acute 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 final level of knowledge

1. The following etiological factors contribute to the occurrence of acute leukemia EXEPT one?
   A. frequent surgery.
   B. ionizing radiation.
   C. retroviral infection.
   D. genetic defects and chromosomal abnormalities.
   E. chemicals.
2. Hyperplastic syndrome in acute leukemia is characterized by all features EXEPT one:
   A. enlargement of lymph nodes.
   B. CNS involvement.
   C. skin pallor.
   D. leukemia cutis.
   E. hepatosplenomegaly.

3. What parameters are characteristic for blast crisis?
   A. the number of blasts in peripheral blood or bone marrow> 30%.
   B. the presence of intermediate forms of blood cells in peripheral blood.
   C. absence of blasts in peripheral blood.
   D. number of blasts in the bone marrow <5%.
   E. agranulocytosis.

4. What is "leukemic gap" phenomenon?
   A. the presence of peripheral blood blast cells, intermediate cells and differentiated cells.
   B. the presence of peripheral blood intermediate cells and differentiated cells and the absence of blast cells.
   C. the presence of blast cells and differentiated cells in the peripheral blood and the absence of intermediate cells.
   D. the presence of blast cells and intermediate cells in peripheral blood and the absence of differentiated cells.
   E. the presence of differentiated cells in peripheral blood and the absence of intermediate and blast cells.

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

6. The contraindications to stem cell transplantation are all mentioned below, EXCEPT one:
   A. acute leukemia.
   B. age over 50 years.
   V. infectious diseases.
   G. systolic heart failure.
   D. severe general condition.

7. What route of cytotoxic drugs application is used to prevent and treat neuroleukemia?
   A. per os.
   B. intravenous.
   C. intrathekal .
   D. intramuscular.

8. What drug is used to prevent the development of kidney stones in patients with tumor lysis syndrome?
   A. fludarabine.
   B. imatinib.
   C. α2-interferon.
   D. allopurinol.
   E. prednisolone.

9. What is the indication for radiation therapy in the acute leukemia?
   A. extramedullary tumor formations.
   B. CNS involvement.
   V. infectious and inflammatory complications.
   G. anemia.
   D. hyperthermia.

10. The signs of suppression of normal hematopoiesis in acute leukemia include all of the following, EXCEPT one:
    A. anemic syndrome.
    B. immunodeficiency syndrome
    C. intoxication syndrome.
    D. hemorrhagic syndrome.

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

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

Case-based questions.

№1.

Patient, 20 years old, had recently finished chemotherapy course due to acute lymphocytic leukemia. What morphological changes of the blood can indicate the onset of full hematological remission?

A. blast cell count below 15%
B. blast cell count below 1%
C. blast cell count below 10%
D. blast cell count below 5%
E. complete absence of blast cells

№2

Patient, 35 years, has been complaining over past 3 months on general weakness, gum bleeding and recurrent nosebleeds, fever up to 38˚C, drowsiness, loss of appetite, weight loss up to 6 kg, night sweats, palpitations and occasional occurrence of dyspnea. Objective data: pale skin, dry tongue covered with white film; painless palpable axillary and neck lymph nodes about 1.5 cm in diameter. Heart rate - 100 / min., regular. Abdomen is soft, slightly painful in epigastric area. CBC: red blood cells - $2,7 \times 10^{12}$ /L; hemoglobin - 82 g / L, CI - 0.95, L - $186,0 \times 10^{9}$/ L; myeloblasts 72%, bands - 4%, segmented 3%, eosinophils 1%, basophils - 1% monocytes - 3%, lymphocytes - 16%, platelets - 106×10^{9} / L. Diagnosis?

A. hypoplastic anemia.
B. chronic lymphocytic leukemia.
C. acute lymphocytic leukemia.
D. chronic myeloid leukemia.
E. acute myeloid leukemia.

№3

Patient, 18 years old, complains on general weakness, fatigue, recurrent nosebleeds, night sweats, fever up to 39˚C, pain in the extremities. She has been sick about a month prior to appointment. Objective data: pale skin, dry tongue covered with yellow film; pain upon percussion of the sternum; painless palpable neck and axillary lymph nodes about 1 cm in diameter, pulse - 112 / min., regular. Abdomen is soft, moderately painful in epigastric area. CBC: red blood cells - $3,1 \times 10^{12}$ / L; hemoglobin - 98 g / L, CI - 0.95, leukocytes $4,8 \times 10^{9}$ / L; blast cells - 22%, eosinophils - 0%, basophils - 0% neutrophils - 46% monocytes - 4%, lymphocytes - 28%, platelets - 118×10^{9} / L. Diagnosis?

A. hypoplastic anemia.
B. chronic lymphocytic leukemia.
C. acute lymphocytic leukemia.
D. chronic myeloid leukemia.
E. acute myeloid leukemia.

№4

Patient, 54 years old, came to hospital complaining on repeated nosebleeds. He's got a history of hypertension over the past 5 years. After measuring the blood pressure an intradermal hemorrhage has instantly formed in the place of cuff imposing. Pulse 104 / min., blood pressure - 140/80 mm Hg. CBC: red blood cells - $3,4 \times 10^{12}$ / L, hemoglobin - 109 g / l, color index - 0.96, leukocytes - $3,9 \times 10^{9}$ / L, blasts - 16%, eosinophils - 0%, basophils - 0% neutrophils - 45%, lymphocytes - 33% monocytes - 6%, platelets - 169×10^{9} / l, ESR - 33 mm / h. Diagnosis?

A. acute leukemia
B. hemorrhagic diathesis
C. hemolytic Anemia
D. chronic lymphocytic leukemia
E. chronic myeloid leukemia

№5

Patient, 27, was diagnosed with acute leukemia. After 3 weeks of chemotherapy the patient's condition deteriorated, an intensive hair loss has appeared, body temperature increased to 39,5˚C, jaundice and bloating or stomach has developed. CBC demonstrated leukopenia, agranulocytosis and thrombocytopenia. Blood cultures - bacteremia. What therapeutic approach should be taken due to the presence of signs of cytostatic disease?

A. radiotherapy
B. immediate splenectomy
C. cancel cytostatics, apply antibiotics.
D. replace polychemotherapy to monotherapy with cytostatics
E. stem cell transplantation

№6

Patient, 27 years old, complains on multiple petechial hemorrhages on the skin and mucous membranes. CBC: hemoglobin - 100 g / L, RBC - 3.1×10^{12} / L, leukocytes - 210×10^{9} / L. Leukemic gap is present. ESR - 46 mm / h. Diagnosis:

A. hemophilia A.
B. leukemic response
C. acute leukemia
D. aplastic anemia
E. everything mentioned above

№7

Patient, 28 years old, was admitted to hospital with complaints on pain in the joints and bones, raise of temperature up to 39,5˚C, general weakness. On examination: pain upon percussion of the sternum, increased submandibular, axillary and supraclavicular lymph nodes. The lymph nodes are mobile, soft, and painless. CBC: RBC - 2.9×10^{12} / L, Hb - 85 g / L, CI - 0.95, L-5×10^{9} / L, platelets - 120.0×10^{9} / L, bands - 2%, segmented,-3%, monocytes 3%, lymphocytes - 24% blasts - 25%, ESR - 55 mm / h. What assay should be necessarily done for the final confirmation of the diagnosis?

A. ultrasound of internal organs
B. chest X-ray
C. sternal puncture
D. lymph nodes biopsy
E. rheumatology blood tests

№8

Patient, 23 years, complains on fever up to 38,5˚C, general weakness. Objective data: enlarged submandibular and axillary lymph nodes, which are soft, flexible, mobile, and painless. Splenomegaly. CBC: erythrocytes - 2.0×10^{12} / L, Hb - 65 g / L; CI - 0.9, platelets - 35×10^{9} / L, L - 3.5×10^{9} / L, segmented - 4%, lymphocytes - 6%, blasts - 90%, ESR - 70 mm / h. What complication is NOT typical for patients with acute leukemia?

A. cachexia
B. turn to chronic leukemia
C. gout
D. brain stroke
E. infections

№9

The patient complains on general weakness, pain upon swallowing, fever up to 39,5˚C. Objective data: hemorrhagic rash on the trunk, enlarged and painless neck and submandibular lymph nodes, splenomegaly, pain upon percussion of the sternum. CBC: erythrocytes - 2.0×10^{12} / L, Hb - 65 g / l; CI - 1, platelets - 32×10^{9} / L, L - 30×10^{9} / L, bands - 2% segmented - 22% lymphocytes - 8% blasts - 68%, ESR - 50 mm / h. In this case, CBC demonstrates the following hematological syndromes EXCEPT of:

A. blasts in CBC differential

B. blast crisis
C. accelerated ESR
D. pancytopenia
E. leukemic gap

№10

Patient, 24 years, complains on general weakness, fever up to 38˚C, pain upon swallowing, gum bleeding, rash on the trunk. Objective data: hypertrophy of the tonsils, stomatitis with ulceration and areas of necrosis; enlarged submandibular, cervical lymph nodes, which are soft, flexible mobile, painless. Complete blood count: RBC - 2,2 $\times 10^{12}$ / L, Hb - 70 g / l; CI - 1, platelets - 70 $\times 10^9$ / L, L - 45 $\times 10^9$ / L, segmented - 18%, lymphocytes - 42% blasts - 40%, ESR - 50 mm / h. What is the cause of tonsillitis in the patient?
A. hyperplastic syndrome
B. anemic syndrome
C. immunodeficiency syndrome
D. intoxication syndrome
E. hemorrhagic syndrome

Correct answers on "Acute leukemia" topic (case-based questions)

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

Control questions.
1. Definition of leukemia.
2. Definition of acute leukemia.
3. Morphological (FAB) classification of acute leukemia.
4. Etiological factors for acute leukemia.
5. Describe the major pathogenetic mechanisms of acute leukemia.
6. List the main clinical symptoms of acute leukemia.
7. List the clinical features of lymphocytic and myeloid leukemia.
8. List the laboratory diagnostic criteria for acute leukemia.
9. Name the list of diseases which should be differentiated with acute leukemia.
10. Describe treatment program for acute leukemia.
11. Characterize prognosis in acute leukemia.

Further reading.

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2. Boyiadzis M., Frame J.N., Kohler D.R. et all. Hematology-Oncology Therapy. - McGraw-Hill Education / Medical; 2 edition (June 26, 2014). – 1888 p.
3. Chisholm-Burns M.A., Wells B.G., Schwinghammer T.L. et al. Pharmacotherapy principles & practice. - The McGraw-Hill Companies, Inc., 2008. – 1671 p.
4. Kasper D.L., Fauci A.S., Hauser S. et al. Harrison's principles of internal medicine: 19th edition. - The McGraw-Hill Companies, Inc., 2015. – 3000 p.
5. Longo D. Harrison's Hematology and oncology. - The McGraw-Hill Education / Medical; 2 edition (April 29, 2013). – 848 p.

6. Merck Manual Professional Version, available at: http://www.merckmanuals.com/professional/hematology-and-oncology/leukemias/acute-leukemia-overview, assessed Aug, 21 2016.