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LEUKOSIS

(a methodological manual for students of the V-VI courses of the Faculty of Medicine, residents and graduate students)

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Compiled by:
prof. Z.T.Astakhova, Associate Professor Z.A.Toguzova, Associate Professor Zh.A.Kulova, Associate Professor Z.Z.Dzukaeva, Associate Professor Zagalova D.S., Associate Professor Avsaragova A.Z., Candidate of Medical Sciences M.M. Besaeva, Candidate of Medical Sciences A.S. Plieva., ass. Gazzaeva S.A., ass. N.O.Kulaeva.

Leukemias are a combined group of blood diseases of a tumor nature, in which the pathological process begins at the level of hematopoietic precursor cells, has a clonal character and is manifested by defects in proliferation (reproduction) and differentiation of hematopoietic elements. They occur with a frequency of 7-8 cases per 100,000 population and, despite undoubted advances in diagnosis and therapy, still have a poor prognosis. According to the nature of the violation of the differentiation of hematopoietic elements and the rate of development of bone marrow failure, all leukemias can be divided into two large groups - acute and chronic. In patients with acute leukemia, the defect in differentiation of hematopoietic elements is maximally expressed, and hematopoiesis is maintained for some time by normal stem cells remaining in the bone marrow. In contrast, in chronic leukemia, the differentiation of hematopoietic cells is less disturbed, which ensures their direct participation in maintaining hematopoiesis and delaying bone marrow failure for several months or years.

Acute leukemia

Acute leukemia (AL) is a disease from the group of hemoblastoses, a malignant tumor of the hematopoietic tissue emanating from the bone marrow, the pathomorphological substrate of which is leukemic blast cells corresponding to the parent elements of one of the hematopoietic lineages.

The term "acute leukemia" was introduced in 1889 by Wilhelm Ebstein to distinguish rapidly developing fatal and relatively slowly progressing chronic leukemias.

Until 1889, OL was considered as a variant of the course of various diseases, and only after sufficient accumulation of clinical and morphological material was it isolated into an independent nosological form.

The OL group is united by a common morphological feature: the tumor substrate is represented by immature young cells - blasts. The name of the forms of OL comes from the names of normal precursors of tumor cells: myeloblasts, erythroblasts, lymphoblasts, etc. OL from morphologically unidentifiable blast cells was called undifferentiated.

Epidemiology. OL occupies a leading place in the structure of the incidence of hemoblastoses, accounting for approximately 1/3 of their total number.

Men get sick with the same frequency as women. At the same time, all researchers note 2 peaks of incidence: at 3–4 years and at 60–69 years.

According to world statistics, the incidence of AL is 3–4 cases per 100,000 population.

Acute lymphoblastic leukemia (ALL) occurs most frequently between the ages of 2–10 years (peak at 3–4 years), then the prevalence of the disease decreases, but after 40 years there is a re-emergence. ALL accounts for about 85% of childhood leukemias. Acute myeloid leukemia (AML), in contrast, is most common in adults, with its incidence increasing with age. The incidence of leukemia among children under the age of 15 is 3.3–4.7 cases per 100,000. About 40–46% of cases occur in children aged 2–6 years.

Etiology. For AL, as for most other tumor diseases, it is impossible to isolate a specific etiological factor. In all likelihood, there is a complex of reasons leading to the development of leukemia.

The virus theory, which arose at the beginning of the last century, is currently receiving new confirmation. In the experiment, it was possible to induce leukemia in healthy chickens by inoculating them with cell-free ultraviolet leukemic tissues of diseased chickens. Despite the significance of these data, which proved the viral nature of leukemia in animals, they are still insufficient to recognize the viral theory of leukemia in humans.

Many supporters have the so-called radiation theory, linking the occurrence of leukemia with the influence of ionizing radiation.

The fact of a significant increase in leukemia among the survivors of the atomic bomb explosions in Hiroshima and Nagasaki has been proven. In these cities, the number of cases of leukemia was on average 11 times higher than in other cities in Japan. Of course, it can be recognized that exposure to ionizing radiation plays a significant role in the occurrence and development of leukemia, and this role boils down to the fact that irradiation of the body causes a mutational effect in the hematopoietic organs, as a result of which blastomatous growth develops. The frequency of mutations depends both on the dose of rays and on the special predisposition of the organism. The radioactive isotopes of carbon and strontium (Sr90) are especially dangerous.

The role of chemical mutagens (especially benzene), including drugs, has been proven.

It has been proven that there is a dose dependence between smoking and the risk of developing acute leukemia, which is especially evident in people over 60 years of age. A number of researchers suggest that in about 20% of cases of AML are the result of smoking. Benzene with prolonged exposure to the human body gives a leukemogenic effect, but at low concentrations of this substance, which people most often encounter at work, the relationship with an increased risk of AL has not been proven.
The works of I. A. Kassirsky served as the beginning for the existence of the so-called theory of innate genetic predisposition.
This theory is based most often on proven violations of endogenous processes in the nucleus, violations of the properties of DNA. Attaching great importance to chromosomal abnormalities in the development of leukemia, it should be emphasized that
that behind them it is necessary to recognize a pathogenetic role, but not etiological. Chromosomal changes are found in approximately 60–70% of patients. It is assumed that they arise under the influence of external adverse factors: ionizing radiation, electromagnetic field, chemicals, benzene, drugs, which include alkylating compounds.
Preschool children, whose bodies have not yet formed, are especially sensitive to the effects of electromagnetic radiation: even just a few hours a week spent at the computer are dangerous for their health. In 1997, data were published in the United States on an increase in the number of children with leukemia, who played computer and video games for more than 2 hours a day.
Pathogenesis The development of leukemia can be represented schematically as a chain of events that begins with a stage of increased mutability of normal hematopoietic cells preceding leukemia, a latent period during which a specific mutation appears in one of these normal cells and a certain gene (or genes) is activated, leading to the appearance of a tumor cell. , to its boundless monoclonal proliferation, which means the development of a benign stage of leukemia in one of the hematopoietic germs. Then repeated mutations occur already in the tumor cell, the selection of specifically mutated autonomous subclones occurs, leading to the progression and formation of a malignant tumor (Burnet's clonal theory).
At the present stage of our knowledge of the pathogenesis of human hemoblastoses, we can formulate the patterns of their tumor progression as follows.
Hemoblastoses, as a rule, go through two stages: monoclonal (benign) and polyclonal - the appearance of subclones (malignant). However, the change of stages occurs with an unequal frequency in different forms of hemoblastoses and with an unequal interval.
The most important feature of hemoblastoses is the inhibition of normal hematopoietic sprouts, primarily the normal homologue of tumor cells.

The change of differentiated cells that make up the tumor in chronic leukemia and lymphocytomas, blast cells, which determine the development of either blast leukemia or hematosarcoma, is regular.

An immunoglobulin-secreting lymphatic or plasma tumor may lose the ability to secrete, which is accompanied by qualitative changes in the behavior of the tumor and usually its blast transformation.

Tumor cells, primarily blasts, can lose the enzymatic specificity of cytoplasmic inclusions and become morphologically and cytochemically unidentifiable.

The shape of the nucleus and cytoplasm of blast cells undergoes abrupt or gradual changes from round to irregular and larger in area.

All extramedullary hemoblastoses (non-leukemic) are capable of leukemia, i.e. metastasize to the bone marrow.

Metastases of hemoblastoses outside the hematopoietic organs reflect the emergence of a new subclone adapted to the given tissue, metastases behave independently in different organs, often they have different sensitivity to cytostatic combinations.

Under the conditions of modern cytostatic therapy, the emergence of tumor resistance to previously effective treatment means a qualitatively new stage in its development. In relapse, the tumor is sometimes again sensitive to the previous cytostatic therapy if the cells of the tumor clone that dominated before the relapse proliferate.

Leukemia can sequentially go through different stages of progression, but sometimes the disease begins with symptoms characteristic of the final stage: with inhibition of normal hematopoietic sprouts, the formation of tumor conglomerates from blast cells in different organs, or with resistance to conventional

cytostatic drugs. In this regard, in the treatment of all leukemias and hemoblastoses in general, in a certain percentage of cases there are failures already at first.

Classification. Given the non-specificity of the clinical manifestations of AL, the diagnosis of the disease is based on the phased application of a complex of laboratory and instrumental studies.

The first stage is the establishment of the fact of the presence of OL using a cytological examination of blood and bone marrow smears.

The second stage is the division of OL into two groups: acute non-lymphoblastic and acute lymphoblastic leukemias. For this purpose, in addition to cytological, cytochemical and immunological studies of the bone marrow are used.

Форма лейкоза	Пероксидаза	Липиды	PAS-реакция	Неспецифическая эстераза	Хлорацетатэстераза	Кислая фосфатаза
Лимфобластная	-	-	+ крупногранулллированная	-	-	в отдельных клетках
Миелобластная	+	+	+ диффузная	слабо +	+	+
Монобластная	Слабо + или отрицат.	Слабо + или отрицат.	+ мелкогранулллированная	+	-	+
Промиелоцитарная	+	+	+ диффузная	+	+	+
Острый эритромиелоз	+	+	+ диффузная	+	+	+
Недифференцированная	-	-	-	-	-	-

The third stage is the division of AL into forms characterized by a certain prognosis and features of therapy. For this, along with the above methods, cytogenetic methods are used (chromosomal disorders are diagnosed in 80% of patients), molecular genetic methods (identification of certain types of translocations, identification of key genes, a method for verifying complete recovery and monitoring the course of residual disease), immunohistochemical, etc.

Differences between ALL and AML are based on the morphological, cytochemical and immunological features of these types of leukemia. Accurate identification of the type of leukemia is of paramount importance for therapy and prognosis.

FAB (French-American-British) classification remains the basis for verification of acute non-lymphoblastic leukemias. The FAB classification of acute lymphoblastic leukemias is currently practically not used in clinical practice due to the lack of its prognostic significance.

Both ALL and AML are in turn subdivided into several variants according to the FAB classification. So, there are three variants of ALL - L1, L2, L3 and seven variants of AML:

M0 - undifferentiated AML;
M1 - myeloid leukemia without cell maturation;
M2 - myeloid leukemia with incomplete cell maturation;
M3 - promyelocytic leukemia;
M4 - myelomonocytic leukemia;
M5 - monoblastic leukemia;
M6 - erythroleukemia;
M7 - megakaryoblastic leukemia.
According to the expressed antigens, ALL is divided into T-cell and B-cell types, which include, depending on the degree of maturity, several subtypes (pre-T-cell, T-cell, early pre-B-cell, pre-B-cell). , B-cell). There is no clear correlation between morphological and immunophenotypic variants, except that the L3 morphology is characteristic of B-cell leukemia.
With regard to AML, immunophenotyping (i.e. detection of expressed antigens) does not always help distinguish between M0-M5 variants. For this purpose, special cytochemical staining is additionally used. For the diagnosis of erythroleukemia (M6) and megakaryoblastic leukemia (M7), immunophenotyping is sufficient.
WHO classification (1979)
This classification is based on the allocation of subgroups of diseases depending on their clonal origin and prognostic significance.
Acute myeloid leukemias.
AML with characteristic cytogenetic translocations:
AML Ct (8;21)
Acute promyelocytic leukemia
AML with abnormal bone marrow eosinophilia
AML with 11q23 (MLL) defects
AML with multilineage dysplasia:
With previous myelodysplastic syndrome or myelodysplasia with myeloproliferation.
Without previous myelodysplastic syndrome, but with dysplastic changes in 50% of cells in two or more myeloid lines.
Secondary AML and myelodysplastic syndrome associated with prior treatment:
Alkylating drugs or radiation
Topoisomerase II inhibitors
Other drugs
AML is no longer categorized:
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblast/monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia
Acute pancyelosis with myelofibrosis
myeloid sarcoma
Acute lymphoblastic leukemia.
ALL from progenitor B cells
ALL from progenitor T cells
Acute leukemia Burkitt
Clinic.
The clinical picture of AL is very diverse. The initial period often proceeds without symptoms or with a small number of them. In some cases, patients complain of general weakness, malaise, sore throat, limbs, joints, headaches. Sometimes patients are concerned about the pallor of the skin, the appearance of bruises. An increase in body temperature is one of the constant signs of leukemia, but the nature of the

temperature curve does not represent anything typical; intermittent type fever is more often observed. Rise in temperature is often accompanied by chills.
Infiltration, loosening and necrosis of the tonsils, covered with a white or dirty gray coating, pain, difficulty swallowing and fever give rise to erroneous diagnoses of tonsillitis, tonsillitis, diphtheria and other diseases. The gums swell, loosen, bleed easily, become covered with dirty-looking granulations, deep ulcers form, spreading to the mucous membranes of the cheeks and palate. Ulcers covered with a dirty coating can penetrate very deeply.
The defeat of leukemic infiltrates of the periosteum of the jaws causes severe pain and loosening of the teeth, as well as prolonged bleeding from the gums. Often, patients fall under the supervision of dentists and are treated unsuccessfully for a long time, until, finally, a blood test clarifies the diagnosis of the disease.
Patients complain of soreness in the bones, especially in the sternum (ossalgia), which is explained by subperiosteal leukemic infiltration.
Shortness of breath often occurs from the very beginning of the disease. It develops, firstly, as a result of the developed anemic syndrome and intoxication, and secondly, as a result of a weakening of cardiac activity.
In the study of the cardiovascular system, there is a small and frequent, sometimes arrhythmic pulse, hypotension. The boundaries of cardiac dullness are expanded, the heart sounds are muffled, and a systolic murmur is often heard at the apex. With significant damage to the heart muscle, you can listen to the gallop rhythm.
The liver and spleen are often enlarged, their consistency is soft on palpation, a slight soreness is determined, occasionally parenchymal or hemolytic jaundice develops.
Manifestations of hemorrhagic syndrome in the form of hemorrhagic rashes can be not only on the skin, but also on the oral mucosa and other organs. Against the background of pale skin, hemorrhages of various sizes appear: from small petechiae to bruises the size of a palm. An extreme manifestation of the hemorrhagic syndrome is bleeding (nasal, gingival, uterine, gastrointestinal), hemorrhages in the brain.
stages of acute leukemia. Leukemia can sequentially go through different stages of development, but sometimes the disease begins with symptoms that are characteristic of the final stage: with the inhibition of normal hematopoietic germs, the formation of tumor conglomerates from blast cells in different organs, or with resistance to conventional cytostatic drugs.
Each stage of development represents a qualitative change in cells, and often only some of them.
1st stage. The first attack of the disease is the stage of extended clinical manifestations, an acute period covering the time from the first clinical symptoms, the diagnosis, the start of treatment to the effect of the treatment. The initial stage of OL is not outlined. Small symptoms of intoxication (fatigue, weakness) are vague, they are not observed in all patients.
Stage 2 - remission. Complete clinical and hematological remission is a condition characterized by complete normalization of clinical symptoms (at least 1 month), blood and bone marrow tests with the presence in the myelogram of no more than 5% of blast cells and no more than 30% of lymphocytes. There may be slight anemia (not less than 100 g/l), thrombocytopenia (not less than 100 • 〖10〗^9/l).
Incomplete clinical and hematological remission is a condition in which clinical parameters and hematogram normalize, but no more than 20% of blast cells remain in the bone marrow punctate.
Stage 3 - relapse of the disease, due to the reversion of the leukemic process to the previous indicators as a result of the release of the residual leukemic cell population from the controlling effect of cytostatic therapy. The clinic is more pronounced than in the 1st stage, and it is more difficult to treat. Blastosis increases in the bone marrow, and cytopenia in the peripheral blood. There may be several relapses according to the number of remissions.
4th stage — complete clinical and hematological remission. It can last more than 5 years. Many authors regard this condition as a recovery, however, relapses of leukemia have been noted after 5, 7, and even 10 years of remission.
The terminal stage of leukemia can be distinguished as the final stage of tumor progression with complete depletion of normal hematopoiesis, resistance to cytostatic therapy.

FEATURES OF THE CLINICAL COURSE OF INDIVIDUAL FORMS

Acute myeloid and myelomonoblastic leukemias

These two leukemias have purely histochemical differences; their morphology and clinical picture are almost the same.

The clinical picture of acute myeloid and myelomonoblastic leukemia is usually due to hematological disorders. A severe onset of the disease with high fever, necrosis in the throat is typical for cases with deep primary granulocytopenia (less than 750-500 granulocytes per 1 µl of blood).

Neuroleukemia occurs in ¼ of cases if it is not prevented. The tumor tissue on the cut has a green color, hence the name of these tumors - chloroma.

Enlarged lymph nodes and organ metaplasia are rare. Leukemids (leukemic infiltrates under the skin) are often observed.

Death can occur at any stage of the process, at any stage of progression, with an exclusively bone marrow lesion - from deep oppression of hematopoiesis, with the spread of tumor growth to different organs - as a result of violations of their activity incompatible with life. A common cause of death in patients is septicemia or other infectious complications caused by cytostatic agranulocytosis, as well as hemorrhagic syndrome caused by deep thrombocytopenia.

The prognosis for this form of leukemia depends on the age of the patient. It is better in younger patients. The frequency of remissions is 60-80%. Life span over 3 years.

Acute promyelocytic leukemia

An independent form of acute leukemia has been identified, which is characterized by a special morphology of blast cells containing abundant coarse granularity, severe hemorrhagic syndrome and rapid flow. The name "promyelocytic" leukemia was due to the outward resemblance of tumor cells to promyelocytes: large abundant granularity fills the cytoplasm and is located on the nucleus, as well as Auer bodies. However, the nucleus of these cells is atypical and in all other morphological features, in particular histochemical ones, they differ from promyelocytes.

In children, this type of leukemia is very rare, in adults in 3.8% of cases.

The course of this type of leukemia prior to the use of treatment regimens containing protransrethioic acid was highly malignant. The average life expectancy after diagnosis was 1 month, as a rule, the main cause of death was cerebral hemorrhage. Currently, the remission rate is about 80%.

Acute monoblastic leukemia

In monoblastic acute leukemia, the process is localized mainly in the bone marrow, but separate groups of lymph nodes and the spleen can be enlarged. Often, infiltration of the tonsils and gums develops, and in the later stages of progression, infiltrates may appear in all internal organs and leukemids in the skin, on the serous membranes.

Blood picture. This leukemia is represented by large blast cells that have a bean-shaped, with a shallow depression, a delicately structural nucleus with several nucleoli; the cytoplasm of these cells is smaller than that of a monocyte, but larger than that of a myeloblast; its color comes in different shades - from gray-blue to intense blue; it often contains scanty dust-like azurophilic granularity. Sometimes such cells are found only in the bone marrow, and in the blood there are more mature elements resembling monocytes, sometimes almost indistinguishable from them. There are cases of monoblastic leukemia with neutrophilia in the blood and with "rejuvenation" of the leukogram to myelocytes. The platelet count usually decreases.

Acute erythromyelosis (Di Guglielmo disease)

clinical picture. In most cases, the onset of acute erythromyelosis is characterized by an anemic syndrome that grows slowly, accompanied by mild icterus. Anemia is usually moderate, not more than 1-5%. The blood picture may also be aleukemic, but as the disease develops, leukemization occurs: either erythrokaryocytes, or blasts, or both, enter the bloodstream. Leukopenia, thrombocytopenia are often observed from the very beginning, sometimes appear later. Bilirubin is usually somewhat elevated due to the indirect fraction.

Unlike previous forms of acute leukemia, where the diagnosis is based on the detection of atypical blast cells in the bone marrow punctate and, therefore, does not present difficulties, in acute erythromyelosis, the punctate often becomes a mystery in itself.

Until an accurate diagnosis is established, no cytostatic treatment can be carried out; small doses of prednisolone, symptomatic therapy - blood transfusion for deep anemia, for example - will not complicate further diagnosis.
The morphology of erythrocytes in erythromyelosis is different. Usually, as in other acute leukemias, despite anemia, there is no anisocytosis, poikilocytosis. If there is anisocytosis, then it is not as sharp as in B12-deficient anemia, there is also no polysegmentation of neutrophils characteristic of it, but gigantism and ugliness of the elements of the granulocytic series are possible. Often there is hyperchromia of erythrocytes with an increase in color index up to 1.2-1.3.
If acute erythromyelosis itself is complicated by increased hemolysis, then the establishment of this particular form of acute leukemia is possible in the presence of a PAS-positive substance in the cells of the red row and blasts, an aneuploid clone (or clones) in the cells of the red row. Without these signs, it is difficult to determine the form. There is no typical organ pathology in acute erythromyelosis. Lymph nodes are usually not enlarged; the liver and spleen, as in other forms of acute leukemia, may increase, but more often remain normal.
Patients with this pathology often have a history of radiation and chemotherapy. The disease affects patients with lymphogranulomatosis, myeloma, erythremia.
Acute megakaryoblastic leukemia
A very rare form of OL. Getting a bone marrow punctate is very difficult because of myelofibrosis. In the blood and bone marrow, along with undifferentiated blast cells, there are also megakaryoblasts: elements with a blast, but a rough and hyperchromic nucleus, a narrow rim of the cytoplasm, which often has an uneven contour due to peculiar processes.
The clinical picture of acute megakaryoblastic leukemia is mostly devoid of specific features. In the outcome of the disease, suppression of normal sprouts of myelopoiesis or sarcoma growth and other signs of the terminal stage are observed. However, in some cases, acute megakaryoblastic leukemia may have a clinical and hematological picture of acute low-percentage leukemia, and according to bone marrow histology, a picture of myelofibrosis. Myelofibrosis and low levels of blasts complicate cytostatic therapy, which exacerbates cytopenia. The most promising and effective treatment for acute megakaryoblastic leukemia with severe myelofibrosis is bone marrow transplantation.
Acute lymphoblastic leukemia
Acute lymphoblastic leukemia often affects children, its peak occurs at 2-4 years; among adults, this form of acute leukemia occurs in 10-15% of patients. The frequency of this leukemia in the population is approximately 2-3 per 100,000 per year.
The peculiarity of the clinical picture of this leukemia in children is the frequent enlargement of the lymph nodes (54%), the spleen (71%). Depending on the location of the primary enlargement of the lymph nodes, the clinical symptoms also change. With their localization in the mediastinum, dry cough, shortness of breath are possible.
The blood picture in acute lymphoblastic leukemia is the same as in other forms. The clinical onset of the disease may coincide with the aleukemic and leukemic phases. Often there are nonspecific changes in the blood associated with a violation of the structure of the bone marrow: single erythrokaryocytes, myelocytes, promyelocytes - signs of myelemia. No matter how confusing the clinical and hematological picture of the onset of the disease, bone marrow puncture, which reveals tens of percent of blasts, resolves all diagnostic difficulties.
The study of T- and B-markers on blast cells of acute lymphoblastic leukemia showed that it is a heterogeneous group. There are at least 3 forms of this leukemia, identified by antigenic markers: acute lymphoblastic leukemia with blast cells that have markers of B-lymphocytes that have markers. T-lymphocytes and not having T- or B-lymphocyte markers (the latter does not mean that they do not contain any antigens). There are very few cases of the B-form of acute lymphoblastic leukemia itself. Leukemia cells with this form are characterized by a high density of IgM on the surface.
Clinically, the features of the T-form of acute lymphoblastic leukemia are more clearly defined. This form is more common in children of the older group, the average age of patients is 10 years, and males predominate among them (the sex ratio is 4:1). The T-form is characterized by an increased frequency of mediastinal lesions in more than 50% of patients, high cell proliferative activity.

The spleen and lymph nodes in acute lymphoblastic leukemia increase for the most part simultaneously with the process in the bone marrow. Unlike acute myeloid leukemia, this increase in this leukemia is not a new stage of progression. Leukemic cells infiltrating the lymph nodes and spleen are usually sensitive to the same cytotoxic drugs as cells in the bone marrow. Without therapy, the course of acute lymphoblastic leukemia does not have any features: inhibition of normal hematopoietic sprouts increases, infectious complications, hemorrhages appear, and anemia progresses.

Metastasis of the process to the testicles and meninges, the most common in children with acute lymphoblastic leukemia, is a new stage (next step) of tumor progression, although it often occurs very early. Extramedullary metastases in this leukemia in most cases have a significantly better prognosis than in myeloblastic. Several years may pass from the onset of neuroleukemia to the death of the patient, during which the therapy maintains the general condition is quite satisfactory. Irradiation of the tumor focus, eliminating it, is not necessarily accompanied by an outbreak of the process in other places and in the bone marrow in the first place.

Acute plasmablastic leukemia

A feature of this form of leukemia is the ability of cells to produce pathological immunoglobulins. Plasmablastic acute leukemia is represented in the bone marrow and blood mainly by plasmablasts, often atypical, and undifferentiated blasts with cytoplasm devoid of basophilia, possibly related to progenitor cells; Plasma cells are also found in the blood. In the blood serum of patients, an M-gradient is detected due to a sharp increase in the production of monoclonal immunoglobulin by leukemic cells.

Diagnostics

Principles of diagnosis of acute leukemia. Diagnosis of AL is based on the assessment of the morphological features of bone marrow and peripheral blood cells. The diagnosis is established only upon detection of the so-called blast cells, characterized by soft reticulation.

the structure of nuclear chromatin, in the bone marrow or peripheral blood. Determining the belonging of tumor cells to the myeloid or lymphoid line of hematopoiesis with the usual Romanovsky-Giemsa stain is possible in approximately 70% of cases. For a more accurate determination, other diagnostic approaches are needed: immunophenotyping, cytochemical, cytogenetic, molecular biological and cultural studies.

Since the mid-70s, the era of modern multicomponent and differentiated therapy for acute leukemia began, which in the late 70s and early 80s made it possible to state the fact that acute leukemia is curable. This made the determination of the exact variant of acute leukemia necessary and fundamental for choosing an adequate treatment strategy. Currently, the most common morphological classification of OL is the FAB classification proposed by the Franco-American-British group in 1976, revised and supplemented in 1991.

In recent years, new methodological approaches to the diagnosis and study of AL have been developed and improved, including immunophenotyping of surface and cytoplasmic markers using poly- and monoclonal antibodies, chromosome analysis, and molecular biological analysis of chromosomal aberrations in ALL and AML.

Using these methods, it has been proven that:

1) acute leukemias are clonal;

2) leukemic cells often carry markers on their surface that characterize certain stages of differentiation of normal hematopoietic cells;

3) aberrant expression of antigens is never determined on normal cells of hematopoiesis;

4) there is a group of OLs whose cells carry markers of different hematopoietic lines (myelo- and lymphopoiesis) or differentiation levels (the so-called early and late markers);

5) during the period of morphologically proven remission, cells with a characteristic leukemic immunophenotype or genotype can be detected.

In this regard, in recent years, several new concepts have emerged in leukemia that reflect the biological properties of OL: clonal remission, minimal residual disease, molecular remission, cytogenetic relapse.

General blood analysis. Blood disorders affect all hematopoietic sprouts. In all cases of AL, sooner or later, normo- or hypochromic anemia occurs. The severity of anemia varies.

The number of leukocytes is subject to large fluctuations. Approximately 40% of patients have severe leukopenia, in other cases there is leukocytosis (even up to 200,000 leukocytes per 1 ml), which can be replaced relatively quickly by leukopenia or a normal number of leukocytes.

Approximately 20% of patients have no blast cells in the hemogram. In most patients, the number of blast forms ranges from a few percent to 80-90%. The cellular composition of the hemogram is often monomorphic, represented mainly by blast cells. Mature granulocytes are detected as single stab and segmented neutrophils.
There are almost no intermediate forms between blast cells and mature granulocytes, which reflects a failure in hematopoiesis - leukemic gaping (hiatus leukemicus).
The number of reticulocytes is reduced or is within the normal range.
Biochemical research methods. When studying the indicators of a biochemical blood test, special attention is paid to the level of lactate dehydrogenase (the norm is 225–460 units / l), especially in ALL, since an increase in the level is an unfavorable prognostic factor.
The level of uric acid can also increase (normal: women - 0.14-0.34 mmol / l; men - 0.2-0.42 mmol / l), while kidney function is impaired up to acute renal failure.
The level of potassium in the blood can both increase and decrease, which also requires correction.
Quite often, hypercalcemia occurs, the cause of which is unknown.
Sternal puncture. Diagnostic value has a study of the bone marrow. The basis for the diagnosis of AL is the detection of more than 30% of blast cells in the bone marrow punctate. The reason for obtaining non-informative punctate ("dry puncture") is often massive foci of spontaneous bone marrow necrosis in acute necrosis. Such necrosis is more characteristic of ALL, they are accompanied by bone pain and indicate a worse prognosis.
Cytochemical research methods. In most patients with AL, cytogenetic studies reveal changes in the state of the chromosomal apparatus, which consist not only in a change in the number of chromosomes, but also in various violations of their integrity. These disorders are specific to each leukemia. In non-lymphoblastic leukemia, karyotype anomalies are observed more often in the 8th and 21st pairs, in ALL - more often in the 4th, 11th or 1st, 19th pairs of chromosomes.
Certain cytogenetic markers are fundamentally important in terms of both therapy and prognosis of the course of acute leukemia.
For example, chromosome 16 inversion is often detected in patients with myelomonoblastic leukemia and high (more than 3%) bone marrow eosinophilia, translocation (15;17) is a typical marker of acute promyelocytic leukemia, translocation (8;21) is observed in 40% of patients with the M2 variant AML. The three described translocations characterize a group of favorable prognosis in AML, and for AML t (8; 21) and t (15: 17) differential treatment programs have been created that allow more than 70% of patients who have achieved complete remission (usually the percentage of achieving remission is with these forms 90-95), live for a long time without signs of relapse.
Translocation 3q21 or 3q26 is typical for myeloid leukemia with thrombocytosis, translocation (6;9) - for AML with basophilia. Both of these options belong to the group of poor prognosis, i.e. even with adequate therapy, long-term relapse-free survival is observed only in 10-15% of patients. Chemotherapy-induced secondary leukemias are very often characterized by pathology of the q23 segment of chromosome 11, and radiation-related leukemias are characterized by changes in chromosomes 5 and 7. The results of treatment of these leukemias are extremely disappointing.
In ALL, it is fundamental to detect translocation (9;22) or (4;11) as a factor of a sharply unfavorable prognosis and hyperploidy, characteristic of ALL variants with a favorable course (most common in ALL in children). Translocation (9;22) is determined in 1-2% of children, and among adult patients - in 25-30%. Translocations that cause poor results in ALL therapy include (8; 14), (2; 8) and (8; 22).
Immunological research method. To determine the histogenesis of tumor cells, an immunological method (immunophenotyping) is used, which reveals antigens (clusters of differentiation) on the cytoplasmic membrane of the cell, indicating the origin of the cell and its degree of maturity.
More than 150 specific antigen proteins were identified on the surface and in the cytoplasm of hematopoietic cells, grouped into so-called differentiation clusters, to which monoclonal antibodies were created, which made it possible to detect them with sufficient accuracy on the surface or inside cells. In most cases, these antigens are surface (membrane) glycoproteins, rarely carbohydrates or glycolipids. Although antigens strictly specific for leukemia cells have not been found, characterization of hematopoietic cells based on a set of antibodies to clusters of differentiation (CD) antigens makes it

possible to determine their linear affiliation and stage of differentiation. The detection of simultaneous expression on a cell of antigens that normally do not occur together allows us to speak of an aberrant (leukemic) immunophenotype.

The tasks of immunophenotyping as a modern diagnostic method include: 1) confirmation of the diagnosis; 2) determination of the AL variant in the case when the cytomorphological method is not sufficiently informative (for example, MO AML); 3) determination of biphenotypic variants of acute leukemia; 4) characterization of the aberrant immunophenotype at the onset of the disease in order to further monitor the minimal residual cell population during the period of remission of acute leukemia; 5) selection of prognostic groups. Each of the CD antigens, using monoclonal antibodies, is detected on normal hematopoietic cells of the corresponding linear affiliation and at certain stages of differentiation. Blast cells are considered positive for the expression of one or another antigen if 20% or more of them express it. Antigens detected on lymphoid cells include CDl, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD9, CD10, CD19, CD20, CD22, CD23, CD56, CD57, myeloid - CD11, CD13, CD14, CDI5 , CD33, CD36, CD41, CD42, CD65, HLADR; the antigen of early progenitor cells is CD34.

A certain combination of these antigens, detected on leukemic cells, allows the latter to be divided within the lymphoid line of differentiation into at least 6 (in some cases 7) subtypes. It is for ALL that immunophenotyping has become a fundamental diagnostic method, since treatment programs for ALL subtypes differ significantly.

In the past 10 years, a differentiated approach to the treatment of different variants of ALL has led to significant advances in terms of long-term outcomes and the characterization of certain risk factors.

With the introduction of the method of immunophenotyping into practice and the creation of a large number of monoclonal antibodies, the concept of "biphenotypic and (or) bilinear" acute leukemia appeared. Most often, we are talking about those cases when leukemic cells carry markers of two or more hematopoietic lines (for example, myeloid and lymphoid). Quite often, the following phenomenon is revealed: morphologically and cytochemically, blast cells belong to a certain line of hematopoiesis, for example, to lymphoid, but during immunophenotyping, markers of the myeloid line are found on their membrane, and vice versa. In such cases, the disease is not classified as a biphenotypic acute leukemia, but is interpreted as an aberrant expression of antigens. Simultaneous expression of markers of the opposite lineage of hematopoiesis occurs in approximately 20–35% of cases of clear AML or ALL. Less often, there are cases when two populations of blast cells coexist, immunophenotypically belonging to different lines of hematopoiesis. This variant of acute leukemia is called bilinear.

The diagnosis of biphenotypic acute leukemia is established in those situations when it is not possible to determine the affiliation of cells to a particular line of hematopoiesis by cytochemical and morphological methods, and during immunophenotyping, fundamentally significant (assessed on a special scale in points) both lymphoid and myeloid are expressed on the membrane of these cells. markers. Only in cases where the combination of markers belonging to opposite lines of hematopoiesis totals 2 or more points for each of the lines present, then only in these cases, acute leukemia is defined as biphenotypic.

The prognostic value of aberrant expression of markers in acute leukemia is not clear enough. It is known that the detection of myeloid markers in both B-cell and T-cell ALL does not affect treatment outcomes. On the contrary, the presence of lymphoid markers in AML is an unfavorable factor in terms of therapy. However, there are reports that the detection of CD2 and CD7 antigens on myeloid cells indicates a favorable course of AML. Time and more multicenter collaborative studies are required to reliably answer the question of the significance of these markers. It is also believed that the results of treatment of biphenotypic AL are significantly worse than those of ALL or AML. Differentiated and standardized treatment programs for these acute leukemias have not yet been created.

Morphological research methods. Morphological examination as a method consists in the detection of undoubtedly blast tumor cells in the blood and bone marrow.

Instrumental research methods. These methods include the study of the function of external respiration, x-ray of the chest, ultrasound of the abdominal organs. ECG allows you to assess the prognosis of the disease and determine the nature of the therapy.

Prognostic factors

The position on prognostic factors in acute leukemia was developed relatively recently - since the advent of adequate chemotherapy, since only when using standard programs it is possible to identify patients with certain clinical, morphological, cytogenetic, immunophenotypic and other characteristics of the disease, in which it is possible or not possible to achieve an effect. . A detailed study of the causes of failure when using standard protocols leads to the formation of risk groups and, accordingly, the creation of new differentiated approaches to the treatment of these patients. Prognostic factors (factors of favorable or unfavorable prognosis) include age, gender, initial somatic status of the patient, clinical, morphological, cytogenetic, immunological characteristics of leukemic cells, etc. It should be emphasized that the presence of an unfavorable prognosis factor in a patient can by no means be the basis for switching to palliative therapy. All prognostic factors are studied and used only in the context of the possibility of such a change in therapy that would increase its effectiveness in patients of this category, i.e. to the disappearance of these risk factors with proper treatment. Thus, the determination of one or another prognostic factor is followed by the need to determine adequate targeted therapy.

The first and fundamental prognostic or risk factor for all patients with any form of AL is adequate chemotherapy. Chemotherapy can be defined as adequate when programs and drugs specifically designed for each specific form of acute leukemia are used, when the doses of cytostatic drugs in these programs correspond to the calculated ones (per body surface area), when the intervals between courses and stages of treatment correspond to the prescribed in the program, when the necessary accompanying therapy is carried out (antibiotic therapy, replacement therapy with blood components), when remission, relapse of the disease is diagnosed in accordance with clear criteria.

The second universal risk factor is the age of the patient. In acute lymphoblastic leukemia in children, the most favorable prognostic age is from 3 to 10 years. In adult patients with ALL (over 15 years of age), the following pattern is observed: the younger the age, the better the prognosis. The worst results were obtained in patients 60 years of age and older. A similar pattern can be traced in myeloid leukemia: in young patients, the chances of achieving complete remission and then long-term survival are significantly greater than in elderly patients.

Many clinical and laboratory indicators are also of great importance, such as the number of leukocytes at the onset of the disease, the level of LDH in the blood serum, the cytomorphological variant of ONLL and ALL, the immunophenotypic, cytogenetic characteristics of each variant of acute leukemia, which allow determining the likelihood of achieving remission, its duration, the likelihood of recurrence, the sensitivity of tumor cells to chemotherapy (further will be considered when describing each form of AL). These factors are many, and their number is increasing with the advent of new research methods.

Treatment

You should never start treatment before the final diagnosis, incl. its morphological subtype. The main goals of AL treatment are the eradication of the leukemic clone, the restoration of normal hematopoiesis and, as a result, the achievement of long-term relapse-free survival of patients. This is achieved through the use of myelotoxic antitumor drugs, which rapidly reduce the volume of the tumor mass, causing deep bone marrow aplasia. It is during the period of aplasia that the so-called state of clonal competition occurs, when cells of a normal hematopoietic clone acquire a proliferative advantage, which repopulate the bone marrow, restoring healthy polyclonal hematopoiesis.

The fundamental principles of chemotherapy of human malignant tumors, incl. and acute leukemias are:

1. Dose-intensity principle, i.e. the need to use adequate doses of cytostatic drugs in combination with strict adherence to time intervals between cycles;

Both experimentally and in clinical practice, it has been proven that a 20% dose reduction in chemotherapy programs leads to a 50% reduction in the effectiveness of treatment. It is also known that a 2-fold increase in the dose in the treatment of tumors with a high growth fraction is accompanied by a 10-fold increase in the number of dying tumor cells. The use of combinations of cytotoxic drugs further increases the percentage of tumor cell death. In this regard, at present, the dose-intensity principle has been supplemented with such a concept as "dose intensity summation", which reflects the influence of many effective and dose-adequate effects on the outcome of malignant tumor therapy.

2. the principle of using combinations of cytostatic agents in order to obtain the greatest effect and reduce the likelihood of developing drug resistance;

Modern chemotherapy for acute leukemia was created empirically, as new cytostatic drugs appeared and the effectiveness of their combinations was studied, as well as based on the laws developed on experimental models.

- Firstly, a mouse model of leukemia made it possible to find a pattern between time intervals, the method of administration of cytostatic drugs and the appearance of clones of leukemia cells that are resistant to the effects of these drugs. In other words, it has been proven that the likelihood of tumor cell resistance is increased with long-term use of drugs at low concentrations and can be reduced by repeated use of pulsed higher dose programs.
- Secondly, the appearance of resistance to chemotherapeutic effects is directly related to the volume of the tumor mass. Therefore, the initial chemotherapeutic effect should be powerful enough to minimize the volume of the tumor mass, and consist in the use of drugs with different mechanisms of action in order to influence leukemic cells of different sensitivity.

3. the principle of staged therapy;

With all OL, there are several stages of therapy:

- induction of remission - the period of initial treatment, the goals of which are the most rapid and significant reduction in the tumor mass and the achievement of complete remission.
- Consolidation of remission - consolidation of the achieved antitumor effect. Currently, in most cases, consolidation is the most aggressive and high-dose stage in the treatment of AL. The objective of this period is to further reduce the number of leukemic cells remaining after induction.
- maintenance therapy
- the use of full complementary therapy, namely the prevention of complications and their treatment. The main preventive measures include:

1. providing vascular access;
2. prevention of infectious complications

The treatment of complications that occur during the period of myelotoxic depression of hematopoiesis requires much more costs than their prevention. The most dangerous complications in 80-90% of patients are of varying severity of infection. The main principle of the treatment of all infections is empirical phased antibiotic therapy with mandatory preliminary bacteriological examination to further change the spectrum of antibiotics used in accordance with the culture results.

- In the early 1990s, hematopoietic growth factors began to be included as adjuvants in chemotherapy research programs for acute leukemia. It has been proven that the use of these factors does not in any way affect the proliferation of leukemia cells (indicators of recurrence-free survival and the duration of complete remission do not worsen). In addition, they significantly reduce the period of myelotoxic agranulocytosis, which in turn leads to a decrease in the number of infectious complications, as well as the number of days of use of antibiotics and antifungal agents. In addition, growth hematopoietic factors are used as priming - enhancing the sensitivity of leukemic cells to subsequent cytostatic effects.
- 3. prevention of hemorrhagic complications with the help of platelet replacement transfusion (at normal body temperature, their level in peripheral blood should be at least 20 thousand, with its increase - 30 thousand).
- Hemorrhagic syndrome was a threat only at the first stages of OL chemotherapy. With the advent of platelet replacement therapy, it occupies a modest place (10-15%) in the list of the most severe complications.
- 4. prevention or treatment of neuroleukemia.
- This stage covers all periods of program treatment - remission induction, consolidation and maintenance treatment. During the induction period, a control and diagnostic puncture is performed with the introduction of one or two drugs, and then three cytostatic drugs are administered prophylactically intrathecally 1-2 times a week. In the treatment of neuroleukemia, cytostatic drugs are administered until the normalization of CSF parameters is achieved and at least three normal lumbar punctures are obtained. An obligatory stage of treatment is head irradiation, which is performed at a dose of 2400 rad after reaching normal CSF levels.
- 5. prevention of massive tumor lysis syndrome - water load, forced diuresis, allopurinol;
- 6. prevention of phlebitis if a central catheter is not used;

- 7. prevention of nausea and vomiting;
- 8. prevention of anemic syndrome - replacement transfusions of er mass (it should be borne in mind that in the absence of signs of hypoxia - shortness of breath during exercise, severe tachycardia, headache, dizziness, fainting, with a hemoglobin level of 75-80 g / l, red blood cell transfusion is not required) .
- 9. prevention of electrolyte disorders
- Treatment should lead to the development of complete clinical and hematological remission:
- • absence of clinical manifestations
- • absence of blasts in peripheral blood
- • less than 5% of blasts in bone marrow punctate
- • absence of extramedullary proliferates
- Incomplete clinical and hematological remission
- • absence of clinical manifestations
- • absence of blasts in peripheral blood
- • less than 30% of blasts in bone marrow punctate
- • absence of extramedullary proliferates
- If the patient does not achieve remission after two courses of induction therapy, then the resistant form of OL is stated. Distinguish between primary and secondary resistance. Primary is the absence of remission after the initial adequate cytostatic effect or early relapse within 6 months from the moment the first remission was achieved.
- Relapse of acute leukemia:
  • bone marrow - the appearance of more than 5% of blasts
  • local - extramedullary proliferation of any localization
  Depending on the mechanism of development, drug resistance is distinguished - due to a change in the metabolism of cytostatics, cytokinetic - due to the proliferative characteristics of leukemic cells: the time of their division or the duration of the cell cycle, and pharmacokinetic - natural barriers (blood-brain), where cytostatics do not penetrate, resistance.
  With the help of the cytogenetic method, the fate of the leukemic clone can be tracked in dynamics. In this regard, the concepts of minimal residual, or residual, disease, "clonal remission" and "molecular remission" appeared.
  Minimal residual disease is usually called the residual population of leukemic cells, which can be detected only with the help of new highly sensitive methods (molecular diagnostics, cytogenetics, etc.), provided that no more than 5% of blast cells are detected in the patient's bone marrow with light microscopy under normal conditions. indicators of peripheral blood and there are no extramedullary lesions. According to modern studies, in most cases, when during the period of remission of acute leukemia it is possible to detect a minimal population of leukemic cells in the bone marrow - a minimal residual disease, a relapse of the disease occurs.
  The recurrence of acute leukemia is fundamentally different from the onset of the disease and should be considered as the emergence and proliferation of a new clone of leukemic cells, most often resistant to ongoing therapy, i.e. due to tumor progression, secondary resistance develops. If an isolated extramedullary recurrence is stated, then in addition to local therapy (treatment of neuroleukemia, irradiation of the testicles, etc.), systemic induction therapy is mandatory.
  Currently, there are three key ALL groups that require different treatment: 1. B-mature ALL; 2. Ph-positive ALL; 3. Ph-negative ALL.
  For the immunologically B-mature variant of ALL (Burkitt-leukemia/lymphoma), it is fundamental to use intense pulsed (block) exposure in combination with anti-CD20 monoclonal antibodies (rituximab). Usually, after completing 4-6 blocks, patients are removed from therapy, they do not receive supportive treatment, they do not need to perform either autologous or allogeneic BMT.
  In Ph-positive ALL, it is necessary to use tyrosine kinase inhibitors (TKIs), starting with imatinib in the first line, with further modification of the targeted effect based on monitoring the minimum residual population of tumor cells and the presence of mutations in the BCR-ABL kinase domain. This impact must be permanent. However, with regard to the amount of chemotherapy in Ph-positive ALL, this is still a matter of debate. Both minimal cytostatic effects (either glucocorticoids alone or glucocorticoids in

combination with vincristine) and more intense ones (classic chemotherapeutic protocols for the treatment of ALL, high-dose pulse protocols) are used. Most researchers consider allogeneic HSCT to be one of the most important stages in the treatment of Ph-positive ALL. In the absence of compatible donors and in the case of achieving molecular remission, autologous HSCT can serve as an alternative to allogeneic HSCT. After any HSCT, TKI treatment should be continued for at least two years after transplantation.

In the treatment of Ph-negative ALL, many programs, especially in adolescents (15-21 years old) and young adults (patients under the age of 30), are oriented towards modern pediatric protocols. A special term has even been introduced to define them as "pediatric based protocols" protocols.

It should be noted that this term is not entirely correct, since all protocols for the treatment of ALL in adult patients, without exception, were borrowed from pediatric studies in the early 1960s. According to modern concepts, protocols "based on a pediatric approach" involve the use of many cytostatic drugs used in the program therapy of ALL at high "pediatric" doses (for example, methotrexate at a dose of 5 g/m2), a "block" multicomponent consolidating effect , accompanied by cytopenias of significant duration (FLAG, CLAEG, HDAra-c + HDMtx) and, accordingly, time without treatment.

In adult patients with Ph-negative ALL, two principles of chemotherapeutic exposure are mainly used: 1) pulsed, high-dose followed by continuous maintenance therapy (the Hyper-CVAD program of M.D. Anderson Cancer Center) and more 2) traditional (standard) - 8-9 -Weekly continuous induction followed by repeated high-dose myeloablative courses followed by maintenance treatment. Also, both approaches provide for a large proportion of patients who are indicated for allogeneic HSCT. The third approach, as previously emphasized, is to reproduce 3) pediatric protocols for the treatment of ALL.

The period of initial treatment, the purpose of which is to significantly reduce the tumor mass and achieve complete remission, is called the remission induction period. In the treatment of ALL, two induction phases lasting 4 weeks each are used, with no break between them. During this period, against the background of the use of cytostatic agents, the number of leukemic cells in the bone marrow decreases by about 100 times, i.e. at the time of ascertaining complete remission in the bone marrow, less than 5% of tumor cells are morphologically determined. When using a pulsed approach (Hyper-CVAD program), two courses are considered an induction stage - the two-week course of Hyper-CVAD itself and the course of high-dose cytarabine and methotrexate following it after a break. In most cases, complete remission is achieved after the first phase of induction (or after the first course of Hyper-CVAD, and only in some patients (10-30%) after the second phase of induction (or the second course of high-dose cytarabine and methotrexate).

The second stage in the treatment of acute leukemia is the consolidation of remission (fixing the achieved antitumor effect). Currently, in most cases, consolidation is the most aggressive and high-dose step in the treatment of ALL. The objective of this period is to further reduce the number of leukemic cells remaining after induction. Most often, 1-2 such courses are provided, then reinduction programs (longer, similar to induction therapy) can be used before maintenance treatment. In the protocol of the Russian group, five long consecutive (3-4 week) stages are called the consolidation period, between which there are no breaks (!), but only the set of drugs used in this period changes and the dosages of a number of cytostatic agents are modified. It should be emphasized that the rotation of the stages of conmolidation provided for by the protocol is possible, depending on the cytopenic syndrome and the variants of complications.

After the completion of the stages of consolidation, a period of maintenance treatment follows, that is, the continuation of the cytostatic effect in lower doses than during the period of induction of remission, on the possibly remaining tumor clone.

Treatment of patients can be carried out in the conditions of inpatient treatment, and in the absence of infectious, thrombotic complications and the absence of myelotoxic agranulocytosis in a day hospital.

For optimal management of patients, especially against the background of long-term constant chemotherapy, it is necessary to provide for the conditions of venous access (addressing the issue of central venous catheterization, installing Hickman catheters or a port system, if necessary).

The main step in the treatment of ALL is the prevention or, if necessary, treatment of neuroleukemia. This stage is distributed over all periods of program treatment - remission induction, consolidation and maintenance treatment. Usually, the prevention of neuroleukemia (the main period is 5-6 intrathecal

injections of drugs) is carried out during the period of induction therapy, then during all stages of consolidation and maintenance therapy, preventive punctures are performed with different frequencies at different stages (on average, the number of preventive lumbar punctures (LP) should be 15-20).

Treatment of neuroleukemia is carried out according to other principles. First, intrathecal injections of cytostatic drugs are carried out with a frequency of once every two to three days until the parameters of cerebrospinal fluid are normalized and at least three normal LP are obtained. Then, punctures for six months are carried out at a frequency of once every two to three weeks, followed by a transition to a prophylactic administration regimen. In most cases, irradiation of the head at a dose of 2400 rad is not required. This approach can be used only in those patients in whom, due to various reasons (anatomical features, extremely difficult tolerability of LP), the prevention of neuroleukemia using intrathecal injections of cytostatic drugs cannot be performed. Also, the question of the use of head irradiation is raised in the refractory course of neuroleukemia (lack of a complete response after 5-6 injections of drugs).

Bone marrow transplant

The problem of using bone marrow transplantation in patients with acute lymphoblastic leukemia remains controversial and still unresolved. Allogeneic bone marrow transplantation can be unequivocally recommended for patients with ALL in the second and later remission, as well as in the first remission from the group with a poor prognosis. Autologous transplantation can be considered as an appropriate therapeutic approach only in the second and later remission. Patients with AML from the standard risk group may be recommended for allogeneic transplantation. There can be no unequivocal recommendations for performing autologous transplantation in AML patients in the first remission. Only under the condition of minimal lethality (no more than 8-10%) due to transplantation itself, autologous BMT can be included in AML treatment programs. For the AML group with a poor prognosis, transplantation does not improve treatment outcomes. This procedure should be performed in specialized centers that perform at least 10 allogeneic and 10 autologous BMT per year. This condition seems to be important, otherwise the lethality in case of complications of the procedure itself will be too high, which will affect the overall survival of patients.

Протокол M.D. Anderson CRC, "Hyper-CVAD/R-HMA "

Протокол Hyper-CVAD состоит из чередования собственно курсов Hyper-CVAD (1,3.5,7) и курса R-HMA - цитарабина и метотрексата в высоких дозах (2,4.6,8) и дальнейшей поддерживающей терапии

Фаза терапии	**Доза, путь введения**	**Время введения**
Hyper-CVAD.		
Циклофосфамид	300 мг/м^2 2 р в день в/в (2-3 ч) (всего 6 введений)	Дни 1-3
Винкристин	2 мг в/в	Дни 4,11
Доксорубицин	50 мг/м^2 в/в (24 ч)	День 4
Дексаметазон	40 мг в/в или внутрь	Дни 1–4, 11–14.
HD-MTX-Ara-C.		
Метотрексат	1 г/м^2 в/в (24 ч);	День 1
Цитарабин	3 г/м^2 2 р в день в/в (2 ч) *Возраст >60 л 1 г/м^2 в/в* (всего 4 введения);	Дни 2,3
Метилпреднизолон	50 мг 2 р в день (всего 6 введений)	Дни 1-3

Профилактика поражения ЦНС проводится на каждом курсе, суммарно 16 интратекальных введений:
Метотрексат – 12 мг интратекально, день 2
Цитарабин – 100 мг интратекально, день 7|

Induction of remission in any form (except for APL) of acute myeloid leukemia should consist of 1 or 2 courses of CT (depending on whether after which course - 1st or 2nd - complete remission is achieved). If complete remission is not achieved after two courses, then primary resistance is established, and patients are treated according to treatment programs for refractory forms of leukemia. Failure to achieve complete remission after the first induction course is a significant factor in the poor long-term prognosis of AML, therefore, immediately after the first course (subject to adequate doses and duration of cytostatic exposure), patients should be considered as potential candidates for allogeneic bone marrow transplantation. If complete remission is not obtained after the first induction course "7 + 3", then the choice of the second induction course can be determined depending on the clinical situation, based on three options: 1) repeating a course similar to the first; 2) change in the intensity of the chemotherapeutic effect - the implementation of a high-dose course; 3) a course of cytarabine in small doses.
Attempts to increase the rate of achieving complete remission by
adding additional cytotoxic drugs to the standard chemotherapy regimen (thioguanine, etoposide, fludarabine, topotecan, etc.) or modulators of multidrug resistance mechanisms did not lead to success.
Options for AML induction courses

Программа индукции	Препарат
7+3(1)	Цитарабин 100 мг/м^2 в/в 2 раза в сутки в 1--7-й дни • даунорубицин 60 мг/м^2 в/в 1 раз в день в 1--3-й дни или • митоксантрон 10 мг/м^2 в/в 1 раз в день в 1--3-й дни или • идарубицин 12 мг/м^2 в/в 1 раз в день в 1--3-й дни
7+3 (2)	Цитарабин 200 мг/м^2 в/в круглосуточно, в 1--7-й дни • даунорубицин 60 мг/м^2 в/в 1 раз в день в 3--5-й дни или • митоксантрон 10 мг/м^2 в/в 1 раз в день в 3--5-й дни или • идарубицин 12 мг/м^2 в/в 1 раз в день в 3--5-й дни
7+3 + VP-16	Цитарабин 100 мг/м^2 в/в 2 раза в сутки в 1--7-й дни Даунорубицин 45 мг/м^2 в/в 1 раз в день в 1--3-й дни Этопозид 120 мг/м^2 в/в 1 раз в день в 17--21-й дни
ADE	Цитарабин 100 мг/м^2 в/в 2 раза в сутки 1-10 дни Даунорубицин 50 мг/м^2 в/в 1 раз в день 1-3 дни Этопозид 100 мг/м^2 в/в 1 раз в день 1- 5 дни
7 + 3 + 7	Цитарабин 100 мг/м^2 в/в 2 раза в день в 1--7-й дни Даунорубицин 45 мг/м^2 в/в 1 раз в день в 1--3-й дни Этопозид 75 мг/м^2 в/в 1 раз в день в 1--7-й дни
ICE	Идарубицин 12 мг/м^2 в/в 1 раз в день в 1, 3, 5-й дни Цитарабин 100 мг/м^2 в/в 24-часовая инфузия в 1--7-й дни Этопозид 100 мг/м^2 в/в 1 раз в день в 1--3-й дни
IVA (1)	Идарубицин 12 мг/м^2 в/в 1 раз в день во 2, 4, 6-й дни Этопозид 100 мг/м^2 в/в раз в день в 3--7-й дни Цитарабин 100 мг/м^2 в/в 24-часовая инфузия в 1--7-й дни
IVA (2)	Идарубицин 12 мг/м^2 в/в 1 раз в день во 2, 4-й дни Этопозид 100 мг/м^2 в/в 1 раз в день во 2--6-й дни Цитарабин 100 мг/м^2 в/в 24-часовая инфузия в 1--6-й дни

Chronic leukemia.

Chronic leukemias are differentiating tumors of the blood system,
the main substrate of which are morphologically mature cells.

Chronic leukemias are the most common hemoblastoses in Europe and North America. So, the share of chronic lymphocytic leukemia (CLL) accounts for 30%, and chronic myeloid leukemia (CML) - 20% of all leukemias.

Classification of chronic leukemia (WHO, 1996)

I. Myeloid forms.

1. Chronic myeloid leukemia.
2. True polycythemia (erythremia).
3. Idiopathic myelofibrosis.

II. lymphoid forms.

1. Chronic lymphocytic leukemia.
2. Paraproteinemic hemoblastoses (multiple myeloma, Waldenström's macroglobulinemia)

Chronic lymphocytic leukemia

Definition. CLL is a tumor of the blood system, the morphological substrate of which is non-proliferating morphologically mature lymphocytes that accumulate in peripheral blood, bone marrow, lymph nodes and spleen.

CLL belongs to the group of lymphoproliferative diseases, characterized by a relatively benign course and slow progression.

Epidemiology. The annual incidence of CLL in Europe and North America is 1.8-3.0 per 100,000 population, accounting for 30% of all leukemias and 9% of malignant tumors. In Europe, about 10,000 new cases of the disease are registered annually. More common in the elderly.

Classification. Currently, there are several classifications of CLL. In the United States, the K.R.Rai classification is the most common, while hematologists of the European school often use the J.L.Binet classification in their practice. In recent years, in different countries of the world there has been a trend towards the combined use of two
classifications, which allows to achieve an adequate interpretation of the diagnosis and treatment results. On the territory of the CIS countries, the classification proposed by A.I. Vorobyov.
1. A.I. Sparrows (1999)
I. By cell substrate:
1. B-cell variant
2. T cell variant
II. By clinical course:
1. Benign form
2. Progressive form
3. Splenic form
4. Abdominal shape
5. Tumor form
6. Bone marrow form
2.K.R Rai (1987)
Stage 0 - isolated lymphocytosis (more than 15.0 G/l in peripheral blood, more than 40% in the bone marrow).
Stage I - lymphocytosis and enlarged lymph nodes.
Stage II - lymphocytosis and splenomegaly and / or hepatomegaly, regardless of the increase in lymph nodes.
Stage III - lymphocytosis, hemoglobin less than 110 g / l, regardless of the increase
lymph nodes and organs.
Stage IV - lymphocytosis, platelet count less than 100.0 G/l, regardless of the presence of anemia, enlarged lymph nodes and organs.
3. J. L Binnet (1981)
A stage - the level of hemoglobin 100 g / l or more, platelets 100 g / l or more, less than three affected areas.
In the stage - the level of hemoglobin is 100 g / l or more, platelets are 100 g / l or more, three or more affected areas.
C stage - the level of hemoglobin is less than 100 g / l and / or platelets is less than 100 g / l.
Diagnostic criteria.
1. Absolute lymphocytosis in peripheral blood more than 5 G/l; in the smear, mature small lymphocytes predominate, the percentage of their precursors (lymphoblasts and prolymphocytes) does not exceed 10.
2. There are 40% or more lymphocytes in the bone marrow.
3. Characteristic immunological phenotype of B-lymphocytes (expression
CD5+CD19+CD20+CD22+CD24+CD25-sIg-CD23+) and T-lymphocytes (expression of CD2+CD3+CD7+CD5+CD4+/-CD8-/+).
4. Expression of κ or λ light chains with a ratio of κ/λ or λ/κ >3.
clinical picture.
In the debut of the disease for many years, only lymphocytosis of 40-50% is possible with a level of leukocytes near the upper limit of normal. Then the lymph nodes gradually increase, starting from the neck, armpits, then - the mediastinum, abdominal cavity, in the inguinal regions.
The main complications of the disease are herpetic infection, infiltration of the VIII pair of cranial nerves with hearing loss, a feeling of congestion and tinnitus, the development of neuroleukemia, exudative pleurisy, the addition of tuberculosis and commonplace infection, transformation into lymphosarcoma (Richter's syndrome).
Blood picture. Lymphocytosis and leukocytosis gradually increase. With almost total replacement of the bone marrow by lymphocytes, it reaches 80-90% in the peripheral blood. Even with leukocytosis of 100 g/l, anemia and thrombocytopenia may be absent.

A characteristic feature is dilapidated nuclei of lymphocytes in a smear - Gumprecht's shadows. As the disease progresses, prolymphocytes and lymphoblasts appear. A large number of them are only in the terminal stage of the disease. In hairy cell lymphocytic leukemia, the cytoplasmic membrane of lymphocytes has outgrowths.

Treatment. Currently used in the treatment of CLL:

1. Monochemotherapy with alkylating drugs (chlorambucil, cyclophosphamide), sometimes in combination with glucocorticosteroids.
2. Courses of polychemotherapy (COR, CHOR, CAP, ROASN).
3. Monochemotherapy with purine analogues (fludarabine, cladribine, pentostatin) or their combination with other cytostatics.
4. Therapy with monoclonal antibodies (alemtuzumab, rituximab).
5. Combined therapy with cytostatics and monoclonal antibodies (immunochemotherapy).
6. Hematopoietic stem cell transplantation, gene therapy, vaccines and other therapies under clinical trials.

When evaluating the effectiveness of treatment, the criteria for response to therapy, developed by the US National Cancer Institute or the International Working Group on CLL, are usually used.

Criteria for response to therapy according to the recommendations of the US National Cancer Institute (Cheson B.D. et al., 1996):

Complete remission:

1. Absence of lymphadenopathy and hepatosplenomegaly.
2. Absence of general symptoms (weight loss, excessive sweating at night).
3. Normal blood counts (granulocyte count ≥1.5 G/l, platelets ≥100 G/l, lymphocytes <4.0 G/l, Hb content >110 g/l.
4. In the myelogram and trepanobioptate, the number of lymphocytes is less than 30%. Lumpy clumps of lymphocytes in a bone marrow biopsy are acceptable.

Partial remission:

1. Reducing the number of peripheral blood lymphocytes by more than 50%.
2. More than 50% reduction in lymphadenopathy and/or more than 50% reduction in spleen and/or liver size + one of the following criteria:

- the number of granulocytes ≥1.5 G/l or an increase of 50% compared with baseline;
- Platelet count ≥100 G/L or 50% increase from baseline;
- Platelet count ≥100 G/L or 50% increase from baseline;
- Hb content >110 g/l or an increase of 50% compared to baseline.

Disease progression:

1. An increase in the diameter of at least two lymph nodes of more than 50% during the last two examinations with an interval of 2 weeks. At least one lymph node must be more than 2 cm in diameter; detection of new palpable lymph nodes.
2. An increase in the size of the liver and / or spleen by 50%; detection of previously absent hepato- or splenomegaly.
3. An increase in the absolute number of peripheral blood lymphocytes by more than 50%, while their total number should be at least 5.0 G/L.
4. Transformation into more aggressive forms of the disease (Richter's syndrome, prolymphocytic leukemia).

Stable state:

There was no complete remission, partial remission, no signs of disease progression.

Therapeutic tactics for patients with CLL consists in the maximum eradication of the tumor clone and an attempt to completely cure young patients, while the goal of therapy in elderly patients is to increase overall and disease-free survival while maintaining a satisfactory quality of life.

The most achievable goal of CLL treatment is to achieve not complete remission, but somatic and social compensation. At the onset of the disease (0-I stage according to Rai), treatment is not carried out, since the appointment of chemotherapy can lead to a shortening of life expectancy due to the addition of infectious complications. Patients are observed by a hematologist with a blood test once every 1-3

months. The results of two large randomized trials conducted in France in 1998 and 2000 showed that the most justified approach to the treatment of CLL in the early stages of the disease in the absence of signs of progression and high risk factors is observation of patients without cytostatic therapy.
The main indications for starting therapy are:
1. Progression of general symptoms associated with the disease (unexplained fever over 38°C for 2 weeks, weight loss over 10%, night sweats).
2. Progressive splenomegaly (more than 6 cm below the costal arch).
3. The occurrence of anemia or thrombocytopenia (both due to bone marrow infiltration and autoimmune genesis).
4. Progressive enlargement of lymph nodes.
5. Progressive lymphocytosis (doubling the number of lymphocytes in less than 12 months).
6. Hyperleukocytosis of peripheral blood (more than 150 g/l).
7. Massive bone marrow infiltration with pathological lymphocytes (more than 80%).
Indications for emergency hospitalization:
1. The development of a severe infection (hospitalization in a hematological hospital is optional).
2. Development of life-threatening cytopenias (deep anemia, hemorrhagic syndrome, neutropenia).
3. The development of CLL complications, including Richter's syndrome, symptomatic lymphadenopathy and organomegaly with a risk of developing severe complications, neuroleukemia, specific pleurisy and chylothorax with signs of respiratory failure, paraneoplastic and autoimmune syndromes, and other life-threatening complications.
4. The development of complications of therapy, including tumor lysis syndrome, severe infusion reactions, myelotoxic agranulocytosis with fever and other life-threatening complications.
It should be emphasized that the lymphocyte doubling period is not an absolute criterion for starting therapy, but if it is less than 6 months, this may be a significant argument in favor of making such a decision.
Alkylating cytostatics have been used in the treatment of CLL for several decades. Their mechanism of action is that they bind to the DNA of the pathological cell and ultimately disrupt its synthesis. The standard treatment for CLL is chlorambucil (leukeran) 4–8 mg/m2 daily for 4–8 weeks, with or without prednisolone 30 mg/m2, while monitoring the white blood cell count. In order to reduce the toxicity and mutagenic effect of the drug, it can be used in the form of 5-7-day cycles. The daily dose of leukeran is 12 mg/m2. In this case, when combining chlorambucil with prednisolone, the dose of the latter should be 40 mg/m2. These cycles must be repeated every month.
In cases with low leukocytosis and a tumor form of the disease, cyclophosphamide is prescribed at a dose of 2-3 mg / kg per day.
In uncomplicated cases, the appointment of glucocorticosteroids should be avoided, as they increase the risk of infectious complications, although they increase the effect of alkylating agents. Glucocorticosteroids are prescribed for autoimmune cytopenias, as well as in cases where it is necessary to achieve a rapid effect from chlorambucil to reduce hepatosplenomegaly or to correct red blood and platelet counts. The dose of prednisolone is 1-2 mg / kg. It is advisable to combine prednisolone with vincristine at a dose of 2 mg intravenously once a week for 3-4 weeks.
In the late stages of the disease, as well as with the ineffectiveness of chlorambucil, polychemotherapy is carried out according to the COP or CHOP schemes.
SOR:
- vincristine 1 mg/m2 IV on day 1
- cyclophosphamide 400 mg/m2 IV on day 1
- prednisolone 40 mg/m2 orally for 5 days
CHOR:
- vincristine 1 mg/m2 IV on day 1
- doxorubicin 25 mg/m2 on day 1
- cyclophosphamide 300 mg/m2 IV on day 1
- prednisolone 40 mg/m2 orally for 5 days
Courses are repeated every 28 days. Patients of a relatively young age (up to 60 years old), insensitive to

chlorambucil, are treated with purine analogues - fludarabine phosphate (Fludara), 2-CdA (Cladribine). Recently, purine analogs have been recommended as first-line drugs, especially in patients with poor prognostic factors. Fludarabine phosphate is administered at a dose of 25 mg/m2 per day intravenously in 200 ml of saline over 30 minutes. The course of treatment is 5 days, it is repeated every 28 days. Cladribine is administered at a dose of 0.12 mg/kg of body weight per day intravenously in 200 ml of saline for 2 hours. The course of treatment is 5 days, it is repeated every 28 days.
After three courses of chemotherapy, response to therapy is assessed according to the criteria of the National Cancer Institute Working Group. If complete remission is achieved, treatment is stopped and the patient is examined every 3 months. If partial remission is achieved, three more courses of treatment with purine analogues are carried out.
With severe splenomegaly, which is accompanied by immune complications, a splenectomy is performed.
Radiation therapy is used for severe local lesions that are insensitive to chemotherapy.
Forecast
In the early stages of the disease, the prognosis is favorable, survival does not differ from that in the population as a whole. In the later stages, life expectancy of more than 5 years is observed only in 40% of cases. The prognosis of the disease depends not only on the stage, but also on a number of other factors, such as the period of doubling the number of leukocytes, the degree of involvement of the bone marrow in the pathological process, the presence of chromosomal abnormalities, mutations of suppressor oncogenes, etc.
Unfavorable prognostic factors
1. Age over 60 years.
2. The presence of general symptoms (fever, sweating, weight loss).
3. Leukocyte doubling time less than 12 months.
4. Diffuse type of bone marrow infiltration according to trephine biopsy.
5. High LDH activity.
6. Increased level of β2-microglobulin.
7. High expression of CD38.
Currently, intensive research is being conducted aimed at studying prognostic factors that would help to clearly divide patients into groups depending on the degree of risk and determine the time of initiation of therapy.
Hairy cell leukemia
Definition. HCL is a chronic B-cell disease characterized by the presence of typical hairy lymphoid cells in the peripheral blood and bone marrow, pancytopenia, and splenomegaly.
clinical picture. The ON course is slow, and its true beginning, as a rule, cannot be established. At the first visit to the doctor, most patients complain of weakness, fatigue, most often due to a decrease in hemoglobin levels. There are frequent complaints of heaviness or slight pain in the left hypochondrium, caused by stretching of the spleen capsule. Rarely, epistaxis or other bleeding associated with thrombocytopenia is the reason for seeking medical attention. In at least 25% of cases, the disease is detected due to frequent infections caused by neutropenia. Indefinite and late-appearing complaints are the reason that only 10-15% of patients with HCL are found in the period when there are no noticeable clinical manifestations. Usually, by the time the diagnosis is established, objective symptoms of the disease are expressed, indicating its long previous course.
The most characteristic clinical symptom of HCL is splenomegaly, which is observed in more than 80% of patients. Of these, in 20% of patients, the spleen protrudes from under the edge of the costal arch by 10 cm or more. In contrast to the very common enlargement of the spleen, enlargement of the liver occurs in only 30-40% of patients, almost exclusively in patients with significant splenomegaly. The liver is almost always slightly or moderately enlarged.
Lymphadenopathy is not characteristic of HCL, and palpable lymph nodes are found in no more than 10% of patients. However, with a computer and ultrasound examination, an increase in mediastinal or retroperitoneal lymph nodes is detected in about a third of patients. In pathological anatomical examination, an increase in mediastinal, abdominal or retroperitoneal lymph nodes is determined in most cases. As a rule, the lymph nodes are slightly enlarged. A significant increase in lymph nodes is more

characteristic of relapse and the terminal stage of the disease. Appearance at
recurrence of massive abdominal lymphadenopathy is a poor prognostic sign. An increase in retroperitoneal lymph nodes is often accompanied by weight loss, abdominal pain, and the appearance of ascites.
Infiltration of nonhematopoietic organs with abnormal cells is even more rare than lymph node involvement.
Described lesions of the skin, soft tissues, lung tissue, pleura, peritoneum, breast tissue. There is a report of sudden loss of vision, which was the first symptom of ON, and resulted from infiltration of retinal capillaries by leukemic cells. Several cases of focal bone destruction similar to osteodestruction in multiple myeloma have been described. The femoral heads are most commonly affected.
Approximately 20% of patients with HCL develop autoimmune complications, but unlike chronic lymphocytic leukemia, autoimmune anemia or thrombocytopenia almost never occurs. Autoimmune complications are manifested in the form of skin vasculitis, arthralgia, arthritis, erythema nodosum. A biopsy of the affected skin reveals perivascular infiltration with lymphocytes, plasma cells, histiocytes, and eosinophils. Leukemic cells do not participate in the formation of perivascular infiltrate, which confirms the nonspecific, but the immune nature of the lesion. Some patients develop a more severe picture with fever, severe malaise, rapid weight loss, damage to the vessels of the lungs, kidneys, and intestines. In these cases, the clinical and histological picture resembles manifestations of nodular periarteritis. Some of these patients can detect antibodies to nuclear DNA, rheumatoid factor, circulating immune complexes.
In mild cases, when only skin lesions and moderate arthralgia are observed, spontaneous regression of the process is often possible. For more severe manifestations of the disease, non-steroidal anti-inflammatory drugs or steroid hormones should be prescribed.
Diagnostic criteria.
1. In the blood test - pancytopenia, in the smear, lymphocytes with an oval nucleus, basophilic cytoplasm with uneven outgrowths are determined.
2. The bone marrow is poor in cellular elements, represented mainly by hairy lymphocytes.
3. In the trepanobioptate - reticular fibrosis, infiltration with hairy cells.
4. In hairy lymphocytes, a positive tartrate-resistant reaction to acid phosphatase is determined.
5. When immunophenotyping of lymphoid cells - a characteristic phenotype
(SmIg+CD19+CD20+CD22+CD5-CD25+CD11c+FMC7+PCA-1+B-ly7+HC2+).
Treatment.
Indications for treatment:
1. Disease progression (decrease in hemoglobin less than 100 g/l, platelets less than 50 g/l, neutrophils less than 1 g/l).
2. Recurrent infection.
3. Damage to the bones.
4. Autoimmune syndrome.
5. Tissue infiltration.
Splenectomy leads to 40% remissions. The main method of drug therapy is the appointment of α-interferon (Intron A, Realdiron, Roferon A). His dose is 3 million IU three times a week for at least 12 months. Complete remission is observed in 5-11% of patients. The drug of choice is cladribine, which can be combined with prednisolone at a dose of 30-40 mg per day. A single course of treatment with cladribine results in complete remission in 95% of cases.

Chronic myeloid leukemia
Definition. CML is a clonal disease of the hematopoietic system with damage to a pluripotent stem cell (not lower than the myelopoiesis progenitor cell), which differentiates to mature forms.
Despite the fact that all three germs of hematopoiesis are affected, mostly uncontrolled growth concerns the granulocytic germ.
Epidemiology. For CML and polycythemia vera, these numbers range from 1-1.5 per 100,000 population. Men 30-70 years old are more often ill.

CML is associated with a specific chromosomal abnormality - the Ph-chromosome (Philadelphia), which is found in 95% of patients. The Philadelphia chromosome was discovered in 1960 in Philadelphia by scientists Nowell and Hungerford. Represents the 22nd chromosome, the deleted segment of the long arm of which is translocated to the long arm of the 9th chromosome.
Classification of chronic myeloid leukemia (Demidova A.V., 1995)
I. Clinical options:
1. Typical (with a Philadelphia chromosome)
2. Atypical (no Philadelphia chromosome)
II. Morphological options:
1. Chronic eosinophilic leukemia
2. Chronic basophilic leukemia
3. Chronic monocytic leukemia
4. Chronic neutrophilic leukemia
III. Phases of the clinical course (stages):
1. Chronic (initial)
2. Accelerations
3. Acute (terminal, blast crisis).
clinical picture.
The initial stage is not diagnosed. The first symptom of the advanced stage is neutrophilic leukocytosis with a shift to myelocytes and promyelocytes. With an increase in leukocytosis above 20-30 G/l, weakness, fatigue, and sweating occur. Heaviness and pain in the left hypochondrium are associated with an enlarged spleen. In the future, the process slowly but steadily progresses (enlargement of the spleen, liver, increase in leukocytosis, decrease in red blood and platelet counts). In the terminal (malignant, polyclonal) stage of the disease, a sudden change in the whole picture of the disease: the rapid growth of the spleen with the development of heart attacks in it, the appearance of fever for no apparent reason, bone pain, the occurrence of anemia, thrombocytopenia with hemorrhagic syndrome.
Picture of blood and bone marrow. In the advanced stage, neutrophilic leukocytosis with a shift to myelocytes and promyelocytes. The number of platelets is often normal, in 20-30% of cases - thrombocytosis. An increase in basophils and eosinophils is possible (basophilic-eosinophilic association). Single blast cells may appear in the peripheral blood without signs of atypia. In the bone marrow there is almost complete replacement with granulocytic cells. Increase in the number of megakaryocytes.
The ratio of leuco/erythro reaches 10:1-20:1. In blast crisis, the number of blasts and promyelocytes in the peripheral blood is more than 30%. In the bone marrow, the number of blasts and promyelocytes is more than 50% of all nuclear elements. With the help of cytological examination and cytochemical reactions, it is possible to establish a variant of a blast crisis (myeloid, lymphoid, mixed).
Criteria for diagnosing chronic phase CML:
1. Leukocytosis more than 30 g/l with a shift in the leukogram.
2. Morphology of granulocyte cells is normal, dysplastic granulocytes are less than 10%.
3. An increase in the number of basophils and eosinophils (basophilic-eosinophilic association).
4. Decrease up to complete absence of activity of alkaline phosphatase of neutrophils.
5. The level of platelets is normal or elevated, but less than 1 million / ml.
6. Hyperplasia of the granulocytic germ of hematopoiesis with a shift to the left in the bone marrow.
7. Hyperplasia of the megakaryocytic lineage in the bone marrow.
8. Reduction of erythrocyte germ in the bone marrow, leuko:erythro index more than 10.
9. Presence of Ph-chromosome in cells of myelo- and lymphopoiesis.
10. In trephine biopsy - hyperplasia of hematopoietic cells with a decrease in fat depot, the presence of reticular fibrosis, hypermegakaryocytosis.
Criteria for diagnosing the acceleration phase of CML:
1. An increase in the number of leukocytes, despite the ongoing treatment.
2. Fever above 38.5°C for a week without signs of infection.
3. Weight loss of more than 2 kg within 30 days.

4. Decreased platelet count by more than 50% of baseline within 30 days.
5. Progressive thrombocytopenia less than 100 g/l.
6. Progressive decrease in hemoglobin level below 90 g/l.
7. Progressive enlargement of the spleen.
8. Increase in the number of blasts more than 10% in peripheral blood or bone marrow.
9. An increase in the number of basophils by more than 20% in the peripheral blood.
10. The appearance of additional cytogenetic anomalies (doubling of the Ph-chromosome, etc.).
Criteria for the diagnosis of blast crisis CML:
1. The number of blasts and promyelocytes in peripheral blood is more than 30%.
2. The number of blasts and promyelocytes in the bone marrow is more than 50% of all nuclear elements.
3. Cytologically or histologically confirmed extramedullary blast infiltrates.
Treatment. The treatment strategy for CML involves two options: palliative therapy, which allows to control myeloid proliferation (hydroxyurea), and therapy aimed at the complete eradication of the leukemic clone, while the ultimate goal is the patient's recovery (bone marrow allotransplantation, hematopoietic stem cell transplantation, imatinib (glivec), alpha-interferon preparations (intron A, realdiron, roferon-A)).
In the chronic phase of CML, hydroxyurea is prescribed at a rate of 40 mg/kg per day, a dose reduction by half is possible after reducing the number of leukocytes to 20 g/l and below, and then the dose is individualized to maintain a normal level of leukocytes.
The optimal dose of α-interferon is 5 million/m2 daily as monotherapy or in combination with small doses of cytosar (10-20 mg/m2 in the first 10 days of the month), the duration of treatment is 10-12 months. Imatinib (Gleevec) is a representative of a new class of antiproliferative agents, signal transduction inhibitors, that selectively inhibit bcr-abl tyrosine kinase.
Indications for bone marrow allotransplantation:
age less than 45 years, early stage of the disease, high or intermediate risk group.
In the acceleration phase, apply:
1. combination of hydroxyurea with low doses of cytosine-arabinoside (50 mg per day) in cycles of 10-15 days.
2. Imatinib (Gleevec) at a daily dose of 400-600 mg for 3-6 months under the control of blood counts.
In case of a blast crisis, PCT regimens are used depending on the crisis variant (Helzer scheme, 7+3, VAD, TAD, etc.). High-dose chemotherapy followed by bone marrow transplantation is not performed due to its unsatisfactory results. It should be noted that there is currently no effective method for the treatment of CML blast crisis.
Idiopathic myelofibrosis (subleukemic myelosis)
Definition. IMF is a chronic neoplastic myeloproliferative disease characterized by early and significant development of bone marrow fibrosis.
The mechanism of induction of myelofibrosis is associated with megakaryocytic germ. It has been established that megakaryocytes synthesize growth factors in excess, stimulating the activity of fibroblasts and collagen synthesis.
Epidemiology. Elderly people and men are more often affected. Cases of the disease at a young age are known.
clinical picture. The course of the disease is usually chronic,
slowly progressive. All symptoms of the disease can be divided into three groups:
1. Associated with a significant increase in the spleen due to its myeloid metaplasia.
2. Due to increased cellular catabolism (weight loss, fever, hyperuricemia).
3. Arising due to bone marrow failure (anemia, thrombocytopenia).
The spleen can reach gigantic proportions, occupying the entire left and right halves of the abdomen. She's thick, bumpy. Subjective sensations - a feeling of heaviness in the abdomen, a feeling of fullness in the stomach, stool disorders, acute pain in the abdomen with spleen infarcts and perisplenitis. More than half of the patients at the time of diagnosis is determined by hepatomegaly. Occasionally there is an isolated enlargement of the liver. as well as the predominance of hepatomegaly over splenomegaly. A significant increase in the liver is usually observed in splenectomy patients.

Liver dysfunction is rare and in most cases occurs in the terminal stage of the disease.
More characteristic is the development of portal hypertension syndrome, which is manifested by a significant increase in the spleen, not due to its participation in hematopoiesis, varicose veins of the esophagus, and then peripheral edema and ascites.
The cause of the development of ascites may be not only portal hypertension, but also implantation of hematopoietic foci on the peritoneum and omentum. In such cases, megakaryocytes and granulocytes are found in the ascitic fluid. This and other atypical localizations of myeloid metaplasia (in lymph nodes with compression of the spinal cord, small intestine, mediastinum, kidneys, and other visceral organs) are among the rarities. There are indications of an increase in peripheral lymph nodes in 32% of patients, but, according to our
observations, this is a much rarer phenomenon.
Symptoms associated with cellular hypercatabolism include weight loss, fever, and hyperuricemia. The latter may be asymptomatic or occur with a clinical picture of gouty polyarthralgia, gout, nephrolithiasis, complicated by chronic pyelonephritis, ureteral obstruction, and chronic renal failure. In some patients, the intensity of stone formation in the kidneys is unusually high. Massive cytostatic therapy with alkylating agents contributes to the development of uricemia.
Although an increase in body temperature may be the result of cellular hypercatabolism, this is true in relation to moderate subfebrile condition, and significant rises in body temperature are usually due to infection, especially of the urinary tract, or latent acute leukemia, which can manifest itself as a typical, unfolded acute leukemia after a number of months and even years.
In cases of quantitative and qualitative pathology of platelets, vascular complications are possible: thrombophilic microcirculatory disorders, thrombosis of arteries and veins, hemorrhagic syndrome, DIC.
Internal bleeding is usually caused by rupture of the veins of the esophagus in the complication of portal hypertension. Inherent in this, as well as in other hMPS, the qualitative defectiveness of platelets explains the appearance of ecchymosis on the skin with relatively moderate thrombocytopenia. The inconsistency of hemostasis is especially clearly manifested during splenectomy.
Anemia often comes to the fore, especially in the later stages of the disease. Its causes, unequal in meaning, are:
1) bone marrow failure;
2) hypervolemia;
3) increased deposition and sequestration of blood cells in the enlarged spleen (hypersplenism);
4) autoimmune hemolysis of erythrocytes;
5) accelerated hemolysis of erythrocytes as a result of PNH syndrome or enzyme defects (deficiency of G-6-FDG, etc.);
6) deficiency of iron and folic acid.
Quantitative insufficiency of erythropoiesis is caused by the replacement of hematopoietic bone marrow with myelofibrosis and osteomyelosclerosis in the presence of adipose tissue. Compensatory erythropoiesis in the tubular bones is reduced over time, and the compensatory possibilities of splenic erythropoiesis are limited by its frequent inefficiency, as well as by the simultaneous increase in the deposition and destruction of blood cells in the large spleen.
Hemodilutional anemia is the result of hypervolemia in splenomegaly. It is well tolerated by patients and is essentially only a laboratory phenomenon.
Defects in the erythrocyte membrane, similar to those observed in paroxysmal nocturnal hemoglobinuria (PNH), have been described in this stem-level neoplastic disease by many authors. Their consequence is the syndrome of hemolytic anemia.
Increased hemolysis of erythrocytes is also promoted by the increase in lipid peroxidation established by us,
Folic acid deficiency leading to the appearance of macrocytic anemia with Cabot rings, basophilic punctuation of erythrocytes, Jolly bodies is observed in the late stage of the disease. It is explained by the increased consumption of folic acid for enhanced hematopoiesis.
Diagnostic criteria:
1. Splenomegaly due to myeloid metaplasia.

2. Collagen myelofibrosis, detected by histomorphological examination of the bone marrow and occupying ½ of the preparation.
3. Leukoerythroblastic picture of peripheral blood with the presence of drop-shaped erythrocytes.
4. The absence of diseases that may be the cause of the development of secondary myelofibrosis.
Blood picture. Leukoerythroblastic: moderate neutrophilic leukocytosis, stab shift, single meta- and myelocytes, erythrokaryocytes, drop-shaped poikilocytes.
Treatment. Indications for cytostatic therapy are thrombocytopenia, leukocytosis, progressive growth of the spleen. The therapeutic dose of hydroxyurea is 0.5-1 g per day, followed by a maintenance dose of 0.5 g per day after 1-2 days. In the presence of cytopenia, splenectomy is preferred. A new direction is the use of α-interferon at a dose of 3 million IU 3-6 times a week.
Polycythemia vera (erythremia, Wakez disease)
Definition. PV is a chronic neoplastic myeloproliferative disease with stem cell damage, proliferation of three hematopoietic lineages, increased production of erythrocytes and, to a lesser extent, leukocytes and platelets.
Epidemiology. The incidence ranges from 0.6 to 1.6 per 100,000 population; 5-6 new cases of the disease are registered annually per 1 million population. Family and ethnic predspolozhennost are established. PV is a disease predominantly of the elderly (the average age of the diseased is 60 years). Cases of the disease in young and even childhood are not uncommon.
Pathophysiology. Abnormal precursor cells are hypersensitive to erythropoietin and some other cytokines. All hematopoietic cells are descendants of the neoplastic clone. Normal residual stem cells are suppressed by the pathological clone. In PV, there is no cytogenetic marker, however, various chromosomal abnormalities are detected in 17-26% of patients.
Classification. Volkova M.A. (2001)
Stage 1 - asymptomatic (initial);
2A stage - erythremic expanded, without myeloid metaplasia of the spleen;
2B stage - erythremic with myeloid metaplasia of the spleen;
Stage 3 - posterythremic myeloid metaplasia with or without myelofibrosis (terminal).
clinical picture.
The onset of the disease is quite variable. In the anamnesis, many patients have indications of skin itching after water procedures, bleeding after tooth extraction, high levels of red blood, peptic ulcer.
An increase in the mass of circulating erythrocytes (MCE) and hematocrit (Ht) leads to an increase in blood viscosity, a slowdown in blood flow, blood stasis at the level of microcirculation, and an increase in peripheral vascular resistance. This explains the high frequency of vascular, mainly cerebral complaints. Sometimes they are in the nature of excruciating migraines with visual impairment. At the same time, many patients have an amazing adaptability to the plethora and no complaints. At the same time, the risk of acute disorders of cerebral circulation remains.
Sometimes the first manifestations of the disease are vascular complications: vein thrombosis, strokes, headaches, necrosis of the fingers of the lower extremities, nosebleeds, decreased vision. Erythrocyanotic coloration of the skin of the hands and face, visible mucous membranes, and soft palate is very characteristic. A sharp contrast in the color of the soft and hard palate is called Cooperman's symptom. The limbs are hot to the touch, the patients feel a feeling of heat.
The cause of splenomegaly in stage 2A is increased deposition and sequestration of blood cells, proven by numerous radiological studies. The degree of enlargement of the spleen in stage 2A is small or moderate. Significant size of the spleen is due to a complication of portal hypertension. This is confirmed by the study of the consequences of accidental splenectomy with unrecognized PV, after which there is a sharp increase in plethoric syndrome, leukocytosis and thrombocytosis.
Liver enlargement often accompanies splenomegaly. In stage 2A it is due to increased blood filling of the liver, in stage 2B it is due to myeloid metaplasia. Both stages are characterized by the development of liver fibrosis, as well as cholelithiasis, the cause of which is the excessive density of bile. Liver cirrhosis is observed as a complication of PV or due to concomitant chronic hepatitis.
At the time of diagnosis, arterial hypertension (AH) is found in 35-40% of patients. Distinguish:
1) symptomatic (plethoric) hypertension, causally associated with an increase in blood viscosity. It is well

controlled by bloodletting;
2) concomitant essential hypertension burdened with plethora;
3) vasorenal hypertension caused by sclerotic or thrombophilic stenosis of the renal arteries (we have several of our own observations).
In some cases, nephrogenic hypertension develops, the prerequisite for which is a complication of urate diathesis and chronic pyelonephritis, as well as impaired microcirculation in the kidneys.
Most patients have signs of impaired uric acid metabolism (stone formation, gout, renal failure).
The picture of the bone marrow is characterized by hyperplasia of three or two hematopoietic sprouts in the myelogram. For differential diagnosis with other erythrocytosis, it is important to detect hyperplasia of a megakaryocyte rather than an erythrocyte germ. The trephine biopsy often reveals an increase in the number of eosinophils, expansion of the bone marrow cavities, thinning of the trabeculae, and growth of reticulin fibers, which retain the correct structure until the evolution of PV into myelofibrosis.
Blood picture. There is an increase in hemoglobin, erythrocytes, leukocytes and platelets in varying degrees of severity, a decrease in ESR. An increase in the mass of circulating red blood cells leads to an increase in hematocrit.
Diagnostic criteria.
1. An increase in the mass of circulating erythrocytes (for men, more than 36 ml / kg, for women, more than 32 ml / kg).
2. Normal saturation of arterial blood with hemoglobin (more than 92%).
3. Splenomegaly.
4. Leukocytosis over 12 G/l in the absence of infections and intoxications.
5. Thrombocytosis over 400 g/l.
6. The index of phosphatase activity of neutrophils is more than 100 units in the absence of intoxication.
7. Increase in unsaturated vitamin B12-binding capacity of blood serum (more than 2200 pg/l).
8. Hyperplasia of the megakaryocytic germ in the myelogram.
IP outcomes.
1. Myeloid metaplasia of the spleen.
2. Myelofibrosis.
3. Typical CML.
4. Acute leukemia.
Treatment. Therapeutic phlebotomy with compensation of BCC with rheopolyglucin, erythrocytapheresis, chemotherapy drugs (hydroxyurea), α-interferon, symptomatic therapy of vascular complications, arterial hypertension and hyperuricemia are used.

Tests
1. The main cause of acute leukemia
1) bacterial infection
2) hypodynamia
3) stress
4) chromosomal disorders

2. Syndromes observed in leukemia
1) painful, dysuric
2) hypertensive, nephrotic
3) hyperplastic, hemorrhagic
4) pain, dyspeptic

3. Leukemic "failure" in the blood test is observed when
1) hemophilia
2) acute leukemia
3) chronic lymphocytic leukemia
4) chronic myeloid leukemia

4. The most common clinical syndrome at the onset of acute leukemia is:
1) Ossalgia
2) Neurological disorders
3) Asthenic condition
4) Hemorrhagic syndrome

5. Hyperplastic gingivitis is typical for the following variant of acute leukemia:
1) Myelomonoblastic
2) Promyelocytic
3) Low interest
4) Plasmablast

6. The classification of leukemias is based on:
1) Clinical picture of the disease
2) Anamnestic data
3) The degree of maturity of the tumor cell substrate
4) Life expectancy of the patient
5) Response to ongoing therapy

6. When identifying forms of acute leukemia, use:
1) Cytochemical method
2) Immunomorphological method
3) Cytogenetic method
4) All listed methods

7. Identification of forms of acute leukemia is based on:
1) Biopsy of the lymph node
2) Sternal puncture
3) Puncture of the spleen
4) Determination of the number of reticulocytes

8. What is the criterion for complete clinical and hematological remission in acute leukemia?
1) the number of blasts in the sternal punctate is less than 5%;

2) the number of blasts in the sternal punctate is less than 2%.

9. The division of leukemia into acute and chronic is based on:
1) The nature of the course of the disease
2) Age of patients
3) The degree of inhibition of normal hematopoietic germs
4) The degree of anaplasia of the elements of the hematopoietic tissue

10. The Philadelphia chromosome (t (9; 22)) in cytogenic analysis can be detected with:
1) Lymphogranulomatosis
2) Chronic myeloid leukemia
3) Acute lymphoblastic leukemia
4) Chronic lymphocytic leukemia
5) Correct 2 and 3

11. The following blood picture: leukocytosis 80 thousand in 1 µl with lymphocytosis (80%), moderate normochromic anemia, normal platelet count, and lymphoid elements in the bone marrow up to 70%, is typical for:
1) Acute leukemia
2) Chronic lymphocytic leukemia
3) Lymphogranulomatosis
4) Multiple myeloma
5) Chronic monocytic leukemia

12. The terminal stage of chronic myelogenous leukemia is characterized by:
1) The emergence of additional new mutant subclones within the main tumor clone, not capable of differentiation, but continuously proliferating, displacing the original differentiating clone of cells
2) The morphology of blood cells and bone marrow does not differ from that in the expanded stage
3) Neuroleukemia is not typical
5) refractoriness to myelosan
6) All of the above

13. Which cells are predominantly part of leukemic infiltrates in chronic myeloid leukemia:
1) myeloblasts
2) myelocytic tumor cells
3) myeloma cells
4) lymphocytes
5) lymphoblasts

14. What cells appear in the blood in the terminal stage of chronic myeloid leukemia:
1) myelocytes
2) reticular
3) myeloblasts
4) Berezovsky-Sternberg
5) myeloma

15. Characteristic changes of organs in chronic leukemia:
1) brown liver atrophy
2) hepatomegaly, splenomegaly
3) cardiac hypertrophy
4) aortic atherosclerosis
5) secondarily wrinkled kidney

16. Characteristics of a fatal complication of acute leukemia:
1) acute heart failure
2) acute renal failure
3) hemorrhage in the brain
4) myocardial infarction
5) pulmonary embolism

17. Chronic myeloid leukemia:
1) is characterized by pancytopenia
2) refers to myeloproliferative diseases
3) occurs in patients with acute myeloid leukemia
18. Which of the complications are typical for chronic lymphocytic leukemia:
1) bleeding
2) infectious
3) thrombotic

19. Specify the symptom that fundamentally distinguishes acute myeloid leukemia from chronic myeloid leukemia:
1) blast cells in peripheral blood
2) vitamin B12 deficiency anemia
3) "leukemic failure"
4) the presence of extramedullary foci of hematopoiesis

20. The term "clonal" origin of leukemias means:
1) acquisition of new properties by cells
2) anaplasia of leukemic cells
3) offspring of a mutated cell
4) variety of forms of leukemic cells
5) all of the above

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