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The Main Complications in Patients with Acute Leukemia during the Period of Myelotoxic Agranulocytosis

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Annotation: *Improvement of chemotherapeutic protocols and algorithms of accompanying treatment made it possible to increase the survival rate of patients with tumors of the blood system. Despite these advances, most of the cytostatic drugs currently widely used to treat patients with hemoblastosis, in addition to the antitumor effect, also cause myelosuppression and the development of granulocytopenia. Granulocytopenia is one of the main factors associated with infectious complications in patients with tumors of the blood system. The nature of infectious complications may differ depending on the duration of granulocytopenia.*

Keywords: *agranulocytosis, immune agranulocytosis, myelotoxic agranulocytosis, acute lymphoblastic leukemias, level of persuasion of recommendations.*

I. INTRODUCTION

Agranulocytosis is a serious pathological condition. With it, a critical decrease in the blood of granulocytes is noted. Granulocytes are an important fraction of the leukocyte series (neutrophils, eosinophils and basophils). At the same time, the concentration of basophils and eosinophils in the blood in a normal state has a small percentage, therefore, a change in their number does not have a significant effect. So, it can be argued that it is a decrease in the concentration of neutrophils that leads to the development of blood agranulocytosis. Hence the second name of pathology - neutropenia.

Experts raise the question of agranulocytosis in a patient with a decrease in leukocytes in the blood below $1 \times 10^9 / L$ and granulocytes below $0.75 \times 10^9 / L$. Since leukocytes and granulocytes perform a protective function against pathogens, a decrease in their concentration reduces the body's ability to resist infections and viruses. The development of agranulocytosis is almost always accompanied by the development of various infectious processes, it can be ulcerative stomatitis or tonsillitis, pneumonia, hemorrhagic manifestations, etc.

Depending on the concentration of granulocytes, the severity of peripheral blood pathology is also determined. The lower their concentration, the harder the degree of all, there are three degrees: mild, medium and severe. In severe cases, the granulocyte concentration indicator is below $0.4 \times 10^9 / L$.

In women, agranulocytosis is more common. In men, this disease is diagnosed on average 2-3 times less often. In most cases, the manifestation of pathology occurs after the age of 40.

Since the pathology has several forms, the symptoms of agranulocytosis of different types differ. The immune type is characterized by acute agranulocytosis with the following symptoms:

- 1) Severe weakness and sweating;
- 2) Body temperature up to $39-40^\circ C$;
- 3) Pallor;
- 4) The appearance of infectious stomatitis;
- 5) Inflammation of the pharynx and tonsils;
- 6) Inflammation of the gums;
- 7) Sore throat and spasm of the chewing muscles.

Myelotoxic and autoimmune types progress gradually and also gradually develop symptoms:

- a) Hemorrhagic symptoms in the form of nosebleeds, bleeding of the gums, etc.;
- b) The presence of blood in the urine;
- c) The occurrence of bruises, hematomas;
- d) Abdominal pain and bloating, diarrhea if the intestines are affected;
- e) Possible chest pain when breathing.

The appearance of agranulocytosis can have different reasons, depending on which the classification of pathology is carried out.

Myelotoxic agranulocytosis is the result of various adverse factors affecting the red bone marrow. Under their influence, a deep depression of the hematopoietic process responsible for the production of granulocytes occurs. Adverse factors should be understood as internal diseases of the body and external adverse influences. Examples of external influences: poisoning with substances and poisons that suppress hematopoiesis (mercury, arsenic, benzene, etc.), radiation exposure, taking myelotoxic drugs. Among the diseases that most often cause agranulocytosis, experts distinguish acute leukemia, sarcoma and metastasis in the red bone marrow, chronic myeloid leukemia.

Immune agranulocytosis - characterized by the destruction of granulocytes in the blood due to the occurrence of pathological immune reactions in the body. This type is additionally divided into the following forms of agranulocytosis.

Autoimmune - occurs in most cases against the background of connective tissue diseases. These include, for example, rheumatoid arthritis or systemic lupus erythematosus.

Haptenic agranulocytosis or drug - develops with the participation of haptens in the immune reactions. Haptens themselves are harmless substances, but in certain situations and reactions they can cause the destruction of granulocytes. The haptens are most often drugs that the patient takes as part of the treatment of various diseases. Hence the second name of pathology - "medicinal".

Genuine - this type is established for the patient in cases where the diagnosis has not revealed the reasons for the decrease in granulocytes in the blood currents.

Myelotoxic agranulocytosis occurs as a result of suppression of the growth of granulocytes in the bone marrow, including stem cells. In this regard, there is a decrease in the blood not only of granulocytes, but also of platelets, reticulocytes and lymphocytes. Myelotoxic agranulocytosis can develop as a result of exposure to ionizing radiation, chemical compounds with cytostatic properties (anticancer drugs, benzene and others), waste products of a fungus such as *Fusarium* that multiplies in overwintered grain

Myelotoxic agranulocytosis can be caused by external adverse effects (exogenous myelotoxic agranulocytosis) and internal diseases of the body (endogenous myelotoxic agranulocytosis). The most common endogenous myelotoxic agranulocytosis is a complication of the following diseases: acute leukemia; chronic myeloid leukemia in the terminal stage; metastases of cancer or sarcoma in the red bone marrow. The development of exogenous myelotoxic agranulocytosis is associated with the fact that, as the most intensively multiplying tissue of the human body, the red bone marrow is especially sensitive to many external factors. The most common causes of exogenous myelotoxic agranulocytosis include: exposure to radioactive radiation; poisoning with poisons that can suppress hematopoiesis (benzene, toluene, arsenic, mercury, etc.); taking myelotoxic medications.

Acute lymphoblastic leukemias (hereinafter - ALL) / acute lymphoblastic lymphomas (LBL) are a heterogeneous group of malignant clonal diseases of the blood system, originating from precursor cells of hematopoiesis predominantly of lymphoid differentiation and characterized most often by initial damage to the bone marrow (hereinafter - BM), displacement normal hematopoiesis and the involvement in the process of various organs and systems of the body (the central nervous system (hereinafter referred to as the CNS), testes, lymphatic tissue of any localization), as well as the possibility of initial damage to the organs of the lymphatic tissue without the involvement of BM [1-5].

Acute myeloid leukemias (AML) are clonal tumor diseases of hematopoietic tissue associated with a mutation in the hematopoietic precursor cell, which results in a block of differentiation and uncontrolled proliferation of immature myeloid cells [1,2].

AML is a consequence of damage (mutation) in the genetic material of a clonogenic hematopoietic cell. As a result, there is a violation of control over the cell cycle, a change in the process of transcription and production of a number of key proteins. Due to uncontrolled proliferation in the absence of differentiation, the accumulation of abnormal cells occurs. The fact that the pathogenesis of OB is associated with genetic breakdowns is quite often confirmed by the detection of various chromosomal aberrations (translocations, deletions, inversions, etc.). In most cases, the exact cause of AML remains unknown.

However, there are several predisposing factors that significantly increase the risk of developing this disease. The clearly proven connection between ionizing radiation during the explosion of an atomic bomb, as well as chemotherapy and radiotherapy for other tumors with an increased risk of OB caused the study of other possible leukemogenic factors (low doses of radiation, chemicals,

smoking, electromagnetic waves). It has been proven that there is a dose relationship between smoking and the risk of developing OB, which is especially evident for people over 60 years of age. A number of researchers suggest that about 20% of AML cases are due to 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 AML has not been proven. When studying the constant exposure to low doses of radiation, no evidence has yet been obtained in favor of an increase in the incidence of OB. For the first time, the relationship between previous chemotherapy, radiation treatment of any other neoplastic diseases and an increased risk of developing AML was noted in patients cured of Hodgkin's lymphoma. It has been proven that not so much the cumulative dose, but the intensity of the dose effect, causes an increase in the incidence of AML. The risk of developing secondary AML is highest in the period from 2 to 9 years after the completion of the previous CT. In 85% of cases, secondary leukemia occurs within 10 years from the end of treatment [1,2]. The etiology and specific factors leading to the development of secondary myeloid tumors are not fully understood. Many genetic pathways and cooperative mutations are involved in pathogenesis. Secondary AML associated with the use of alkylating drugs often debuts with myelodysplastic syndrome (MDS) with monosomy or partial deletion of chromosomes 5 and 7. This type of AML occurs relatively late, on average 5–7 years after the primary tumor has been treated. Appendix A3.6 provides a description of secondary AML associated with topoisomerase II inhibitors and alkylating agents.

It is recommended to start AML induction therapy immediately.

After all diagnostic activities have been completed. It is permissible to postpone the initiation of chemotherapy until the results of all laboratory tests are obtained, which will allow a more detailed characterization of the disease and determine the correct therapy tactics [4,44].

The level of persuasion of recommendations - B (level of evidence - 3) Comment: delaying the initiation of therapy for a short period (5–7 days) from the beginning of diagnosis of the disease does not affect the effectiveness of therapy, early mortality rates, and long-term results of AML therapy.

It is not recommended for patients with AML to start cytostatic therapy immediately if the patient has:

- Severe congestive heart failure (ejection fraction less than 50%), unstable angina pectoris, gross rhythm and conduction disturbances with hemodynamic instability, acute myocardial infarction (history less than 1 month);
- Renal failure (serum creatinine index > 0.2 mmol / l (or > 200 mg / μ l), except in cases caused by leukemic renal infiltration);
- Liver failure (except for cases caused by leukemic organ infiltration), acute viral hepatitis B or C;
- Severe pneumonia (respiratory failure - shortness of breath > 30 respiratory movements per minute, arterial hypoxemia < 80 mm Hg. Art. because often the initial lesion of the lung tissue is diagnosed leukemic cells, and without specific therapy the chances of a cure for pneumonia are extremely small);
- Sepsis (with hemodynamic instability); only high fever without characteristic signs of sepsis cannot serve as an excuse to postpone HT;
- Life-threatening bleeding (gastrointestinal tract, profuse uterine, cerebral hemorrhage);
- Severe mental disorders (delirium, severe depressive syndrome and other manifestations of productive symptoms);
- Physical disability requiring constant care, cachexia (total protein index < 35 g / l);
- Decompensated diabetes mellitus (blood glucose level > 15 mmol / l);
- Uncontrolled course of concomitant cancer [1].

Strength of recommendations - C (level of evidence - 5)

Commentary: if at the time of admission the patient had one of the above conditions, but it can be stopped or controlled as a result of intensive symptomatic treatment, then the patient can be started cytostatic chemotherapy after 3–7 days. If in the course of symptomatic treatment of concomitant pathology, AML progresses in the form of an increase in the number of leukocytes, the percentage of blast cells in the peripheral blood, or the initial level of leukocytes is $100 \times 10^9 / L$ or more, it is advisable to add # hydroxycarbamide to the treatment of complications at a dose of 100 mg / kg per day [6] and / or leukocytapheresis and, if necessary, perform plasmapheresis to prevent tumor lysis syndrome. If the patient's condition, due to extremely severe complications associated with the disease, or due to severe concomitant pathology, cannot be stabilized within a maximum of 7 days, it is allowed to consider a palliative cytostatic effect (for example, cytarabine in low doses).

Recent studies at the genetic level have made it possible to develop tests that can be used to quite accurately determine the probability of patient survival and the effectiveness of a particular drug for an individual case of AML.

Granulocytopenia is a predictor of the development of infectious complications in patients with AML and ALL. Thus, the proportion of infections during the period of granulocytopenia is 80%, and outside granulocytopenia - only 6%. A correlation between the duration of granulocytopenia and the frequency of infections is found in ALL patients, while there is no such relationship in AML patients. The frequency of infections in patients with ALL increased from 25–33 to 91% with an increase in the period of granulocytopenia from 1–14 to 22 days or more, and in patients with AML it was high for any duration of granulocytopenia and amounted to 92–100%.

With the lengthening of granulocytopenia, the nature of infectious complications changed. Both in AML patients and in ALL patients with granulocytopenia up to 2 weeks, LNE, CDI and bacteremia prevailed in the spectrum of infections, and with granulocytopenia from 28 days or more, the likelihood of developing IA significantly increased, which reached 66% by the 55th day of granulocytopenia.

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