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Clinical Manifestations of Cardiotoxicity in Acute Leukemia and Methods for their Examination

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Abstract: Currently, more and more attention is paid to cardiotoxicity, which develops against the background of anticancer treatment. Achievements of modern oncology are associated with the use of effective combinations of chemotherapeutic drugs and radiation therapy, at the same time, some of the commonly used drugs, as well as radiation therapy in some patients, leads to the development of various complications.

Keywords: acute leukemias, The European Group of Leukemia Immunology, chronic heart failure, therapy, monitoring, cardiotoxicity.

There are several classifications of acute leukemias based on morphological, immunophenotypic, and genetic criteria. Until now, the Franco-American-British (FAB) classification, proposed in 1976 and supplemented in 1985, is relevant and generally accepted. It provides for the division of acute leukemia into lymphoblastic and myeloid based on the morphological characteristics of tumor cells (Auer rods, the nature of intracytoplasmic granules, the presence of signs of cell maturation, the shape of the nucleus, the basophilicity of the cytoplasm).

Approximately 85% of children with ALL have an L1 morphology, 14% have an L2 morphology, and 1% have an L3 morphology. The most frequently diagnosed variants in children with AML are M2, M4 and M5 (approximately 20-22% each), followed by the M3 variant (approximately 10-13%) in frequency of occurrence. Unfortunately, the morphological features of tumor cells give us far from complete information about the types of AL, and most importantly, they do not allow us to clearly orient ourselves in the choice of treatment tactics and assess the prognosis for a particular patient. This is especially true for ALL in children, where the morphological classification of FAB currently has more historical than practical significance.

Immunophenotypic study based on the determination of a set of markers on the surface of tumor cells is a defining moment in the diagnosis of acute leukemia, their classification in accordance with the belonging of cells to T - or B-lines and the degree of their differentiation. The distribution of acute leukemia according to immunophenotypic characteristics underlies the implementation of optimal risk-adapted modern therapy and determining the prognosis of leukemia, especially in the case of ALL and for the differential diagnosis of some variants of AML. The development of monoclonal antibodies conjugated with fluorescent dyes and targeted to specific molecules on the cell membrane (CD molecules or differentiation clusters) and cytoplasmic antigens has revolutionized the biological classification of acute leukemias. The European Group of Leukemia Immunology (EGIL, 1995) has developed an immunological panel of antibodies to CD molecules, which makes it possible to clearly determine the linear affiliation of leukemic cells and the level at

which their maturation was stopped. The study is carried out by flow cytometry, which allows you to automatically calculate the number of labeled cellular elements. The set of tumor cell markers determined using this method is called the immunophenotype. In ALL, there are 4 groups of B-linear subtypes of leukemia (pro-B (BI), total-B (BII), pre-B (BIII) and mature B (BIV)) and 5 groups of T-linear (pro-T (TI), pre-T (TII), cortical T (TIII), mature T (TIV), and the recently described early progenitor T) depending on the degree of maturity of the leukemic cells. For the diagnosis of ALL, it is important to determine the so-called early markers present on undifferentiated lymphoblasts (CD34, CD10), B- (CD19, CD20, CD22) and T-cell antigens (CD3, SD5, SD7, SD4, SD8). In the case of AML, it is necessary to determine the antigens of blood stem cells (CD34), myeloblasts and monoblasts (CD13, CD33), megakaryoblasts (CD61), erythroblasts (CD235 or glycophorin A, CD71).

B-linear leukemias account for 80% of all childhood ALL leukemias. At the same time, total-B ALL, characterized immunophenotypically as DM10+DM19+, is the most common subvariant.

Immunophenotyping in AML, with the exception of variants M0, M6 and M7, has no significant diagnostic value. At the same time, careful characterization of the leukemic cell phenotype is necessary to monitor the effectiveness of therapy and monitor minimal residual (residual) disease in patients who have achieved clinical and hematological remission. In M0, M6 and M7 variants of AML, immunophenotyping, on the contrary, provides significant assistance in establishing the correct diagnosis.

In 2001, the World Health Organization (WHO) attempted to propose a classification based on genetic changes in leukemia cells that determine the therapeutic approach to the patient and his prognosis for recovery. Unfortunately, this classification turned out to be quite cumbersome, inconvenient in practical terms, and applicable only to countries with a developed system of molecular genetic laboratories.

The WHO classification accurately identifies different therapeutic groups to determine the disease's prognosis. Variants of AML with t (8; 21), t (15; 17), inv 16 are characterized by a relatively favorable prognosis. At the same time, variants of AML with MLL 11q23, secondary AML and AML with multilinear dysplasia are characterized by an extremely unfavorable prognosis, despite chemotherapy according to modern protocols and require allogeneic hematopoietic stem cell transplantation. In ALL, the worst prognosis is observed in cases of the presence of the Philadelphia chromosome (t (9; 22) (q34.1; q11.2); BCR-ABL1 gene) and in cases of ALL with rearrangement of the MLL / AF4 gene at t (4; l 1) (q21; q23) in children under 1-year-old. At the same time, ALL with t (12; 21) and hyperdiploid variants, in which the number of chromosomes in tumor cells is increased, respond relatively well to treatment.

Summing up, it can be noted that the optimal clinical classification of ALL, which determines the therapy and prognosis of the disease, is based on the immunophenotyping of bone marrow blasts, while morphological methods are more important for AML. Molecular genetic studies are of leading importance for all acute leukemias, regardless of phenotype.

While the main "classic" causes of chronic heart failure (CHF) are ischemic heart disease (post-infarction cardiosclerosis, chronic post-infarction aneurysm), arterial hypertension and their combination, cardiomyopathy (CM, most often dilated) and myocarditis, increasingly in various recommendations According to the diagnosis and treatment of heart failure (HF), toxic and radiation effects on the myocardium are mentioned as its etiological factor [5, 3].

To date, a large number of cases of cardiac complications have been described that develop against the background of the administration of anthracycline antibiotics, which is associated with their high antitumor activity, as well as their wide use in various chemotherapy regimens [1; 2; 4; 6]. For a long time, there was a hypothesis that the cause of anthracycline CMP (ACMP) is the formation of an excess of reactive oxygen species (reactive oxygen species, ROS) due to the exchange of electrons between the quinone moiety of anthracycline and oxygen molecules and other electron donors present in cells. Anthracyclines also form complexes with iron, which undergo redox reactions that generate oxygen radicals.

At the moment, there is no single classification of cardiotoxicity of chemotherapeutic drugs, which can develop at different times from the start of treatment.

Primary prevention of cardiotoxicity is based on two strategies:

1. Reducing potential cardiotoxicity: the use of long-term infusion of drugs, the use of its liposomal forms, and the use of less toxic derivatives (for example, epirubicin or idarubicin).
2. The use of cardioprotective agents: dexrazoxane, beta-blockers, ACE inhibitors, angiotensin II receptor blockers during polychemotherapy [3].

For early detection of signs of cardiotoxic damage to the cardiovascular system and the appointment of the necessary therapy for patients with malignant diseases, an extended examination and joint monitoring by oncologists and cardiologists is recommended. Examination of patients must be carried out without fail before the upcoming treatment, during its implementation and for many years after its completion - taking into account the complications that develop in the long term, dynamic monitoring of these patients should be virtually lifelong.

Treatment of acute leukemia in children should be carried out only by trained and highly qualified personnel in specialized institutions with laboratory facilities, an intensive care unit, and a modernly equipped blood transfusion service.

The treatment of acute leukemia in children is based on complex drug therapy, which, as in the treatment of other oncological diseases, is determined by the treatment protocol. The protocol is a medical document that defines the terms, doses, method and conditions for the administration of a particular chemotherapeutic drug, the combinations of chemotherapy drugs used, the procedure for conducting accompanying therapy, the list of mandatory studies both for primary diagnosis and for evaluating the effectiveness of treatment (definition of MRR). The protocol also defines the methods and procedure for monitoring the patient at the outpatient stage. Depending on the frequency of occurrence in children of one form or another of acute leukemia, there are international and national protocols that unite a number of oncohematological clinics and centers. One of these clinics assumes the responsibility of a research center for a specific nosological form of the disease, collects, scientifically and statistically processes information on the treatment of each patient, provides consultations, references diagnostic tests, develops protocol updates based on empirical data, experience gained and the results of modern basic research. Another important function of the research center is the randomization of patients. According to the condition of a number of protocols, patients with a similar diagnosis and clinical condition may receive different treatments at different stages. The obtained results of treatment in different groups are compared and used to improve the protocol.

All of the above pose new challenges for cardiologists and therapists: knowledge of the manifestations of cardiotoxicity, taking measures to prevent them, and timely detection and treatment of cardiotoxicity developing during or after the end of cancer therapy.

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