Course And Management of Patients with Acute Promyelocytic Leukemia on The Background of Cytostatins

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ABSTRACT

The number of patients who achieved complete remission, as well as the mortality rates during remission induction were wholly comparable to those previously obtained when using the 7+3+ATRA protocol: 90.3 and 9.7%, respectively. One patient in remission died (3.6% mortality rate). The likelihood of recurrence in this investigation was high (21%), which was due to gross noncompliance with maintenance therapy. On examining the clearance of the malignant clone by FISH and polymerase chain reaction, a naturally chimeric transcript identified by a molecular study was statistically significantly more frequently revealed during postinduction therapy, which was associated with different sensitivity of the techniques. Comparison of changes in the disappearance of a chimeric marker for APL with the AIDA and 7+3+ARTA programs showed that the clearance of the malignant clone was much slower.

Keywords: Acute promyelocytic leukemia, idarubicin, all-trans retinoic acid

Introduction. Acute promyelocytic leukemia – OPL (according to the WHO classification 2008 – acute myeloid leukemia with t(15;17)(q22;q12); (PML-RARa) and variants; according to the FAB classification - M3, M3v – atypical OPL) is attributed to a rare, special form of acute myeloid leukemia (5-15% of all cases AML.). It is characterized by an abnormal accumulation (≥20%) in the bone marrow of one of the types of myeloid cells – promyelocytes in combination with chromosomal translocations affecting the alpha gene of the retinoic acid receptor (RARa) located on chromosome 17. In turn, promyelocytes are granulocyte progenitor cells that arise at one of the stages of their maturation (myeloblasts – promyelocytes - myelocytes – granulocytes) [1].

The main chromosomal anomaly of OPL (95%) is a reciprocal translocation of (t) (15;17) (q22;q21) - PML/RARa in tumor promyelocytes, as a result of which the promyelocytic leukemia gene (PML gene) located on chromosome 15 is transferred to the long arm of chromosome 17 in the region where the gene is located alpha-retinoic acid receptor (RARa). As a result of t (15;17), a pair of merging abnormal genes appears: PML/RARa on the derivative (der) of chromosome 15 and RAR/PML on the derivative of chromosome 17.

Factors that can cause mutation of hematopoietic tissue cells leading to OPL: hereditary predisposition to cancer, immunodeficiency conditions, certain types of viruses, medications, ionizing radiation, chemical carcinogens, mechanical damage to tissues, obesity, etc.

OPL occurs at absolutely any age, even in childhood. However, most patients at the time of diagnosis of the disease are about 40 years old, which is a distinctive feature of OPL from other types of acute myeloid leukemia, where mostly patients are elderly people.

Usually, OPL, like other types of acute leukemia, is characterized by such manifestations as anemia (shortness of breath, fatigue, weakness), thrombocytopenia (bleeding, bruising and bruising), as well as leukopenia (decreased body defenses, infectious diseases). In addition, bleeding associated with DIC (disseminated intravascular coagulation syndrome) is observed in OPL.

Diagnosis and treatment of OPL in Russia and abroad is carried out according to national clinical guidelines for program protocols [3, 4, 5].

The purpose of the study. To review the literature on the problem of diagnosis and treatment of acute promyelocytic leukemia. To compare the effectiveness of treatment protocols and the possible toxicity of chemotherapeutic drugs used.

Material and methods of research. To compare the world practices of the treatment of OPL, more than 30 scientific and practical articles devoted to this problem and published in various medical journals in the period 1997 - 2019 were studied and analyzed.

Modern protocols for the treatment of OPL by both Russian and foreign oncologists are basically similar and include schemes for the combined use of ATRA and/or ATO drugs and anthracycline antibiotics with or without cytarabine.

The results of the study and their discussion.

OPL is diagnosed on the basis of morphological, cytochemical, cytogenetic, molecular genetic, immunophenotyping analysis of a bone marrow sample [1].

According to initial peripheral blood tests, all patients are stratified according to the M. Sanz scale:

1. Low risk group: leukocytes ≤ 10x109/l, platelets ≥ 40x109/l;
2. Intermediate risk group: leukocytes ≤ 10x109/l, platelets □ 40x109/l;
3. High-risk group: leukocytes > 10x109/l [3].

According to the generalized data of scientific and practical monographs, low-risk patients account for 26%, medium – 52% and high – 22% of the total number of patients with OPL.

Previously, OPL was classified as a leukemia with a very unfavorable prognosis. But modern methods of program treatment of OPL – the use of specific drugs – completely transretinoic acid (ATRA) and arsenic trioxide (ATO) in combination with polychemotherapy, allow to achieve high survival rates of patients without the use of cytostatic drugs in 80-95% of cases.

While taking ATRA, leukemic promyelocytes are "reprogrammed" to further transform them into mature granulocytes. However, it is worth noting that against the background of taking ATRA, even if cytostatic drugs are administered, there is always a possibility of developing retinoid syndrome (MS), or tumor cell differentiation syndrome (febrile fever, shortness of breath, signs of acute renal and / or hepatic insufficiency, fluid retention).

At the slightest signs, even with the slightest suspicion of the development of MS, the patient is prescribed dexamethasone 10 mg / m2 2 times a day. Usually, the signs of retinoid syndrome are stopped very quickly, so long-term therapy with dexamethasone is not indicated. Withdrawal of ATRA is usually not required, however, in the case of severe MS, the drug can be canceled before the cupping of MS. Its intake can be resumed in half doses [4,7].

In cases of insufficient efficacy or intolerance of the drug ATRA, relapse of the disease and as an independent drug for the treatment of OPL, ATO (arsenic trioxide) is used, which is characterized by high efficiency with moderate toxicity. According to scientific sources, the frequency of achieving complete remission with arsenic trioxide treatment is 86%.

Among the possible side effects of ATO, it should be noted a differentiation syndrome similar to the retinoic acid syndrome mentioned above; heart rhythm disturbance is less common. It should be noted that due to the high embryotoxicity of arsenic trioxide, its use for the treatment of OPL in pregnant women is strictly prohibited at any stage of pregnancy.

The frequency of complications in hemoblastosis polychemotherapy ranges from 80% or more cases, and deaths reach up to 10% [2,8].

OPL is a deadly disease and if not treated, patients die within a few weeks, sometimes even a few days.

In all cases of suspected OPL (the presence of a characteristic morphological picture of blast cells, leukopenia, severe coagulopathy, hemorrhagic syndrome), ATRA therapy should be started immediately and continued until the diagnosis is confirmed or refuted based on molecular genetic research.

In the treatment of OPL, there are four main stages of treatment.

Stage 1 – induction (achieving remission). The patient is undergoing intensive therapy with chemotherapy drugs for the greatest reduction in the number of malignant cells (5-8 weeks). The stage of induction therapy is complex and requires adequate massive accompanying therapy (antimicrobial, hemotransfusion, antiprotozoal, antiviral, antifungal, etc.), as well as the jurisprudence of prevention and treatment of retinoid syndrome. During the induction period, a control and diagnostic puncture is performed for hematological control of remission.

Stage 2 – consolidating (consolidation of remission). Consolidating therapy is based on the potential risk of relapse in patients who have undergone induction therapy. Its primary goal is to transform morphological and cytogenetic remission into long–term molecular remission, by destroying the remaining leukemic cells after remission induction with a new combination of chemotherapy drugs, within 2-4 months.

Stage 3 – supportive. Continuation of the effect of chemotherapy drugs on the preserved tumor clone. Reception of maintenance therapy is prescribed, according to different protocols of treatment of OPL, from 150 to 180 days of treatment and lasts 2-3 years. With gross violations of the maintenance therapy regime, the likelihood of relapse is very high.

Stage 4 – prevention of neuroleukemia. This stage is distributed over all periods of OPL treatment [4].

Induction treatment of OPL requires massive transfusion therapy with thromboconcentrates (it is necessary to maintain platelets at 50x109 / l and above) and freshly frozen plasma or cryoprecipitate (fibrinogen level is more than 2 g / l, prothrombin index is more than 80%). The use of ATRA did not cancel aggressive replacement therapy with blood components, but only slightly reduced the volume of transfusion agents used. Invasive procedures, such as the installation of a central venous catheter (CVC) or lumbar puncture, should also be avoided in order to avoid thrombohemorrhagic complications [5].

With hyperleukocytosis (especially more than 50x109 /l) against the background of a chemotherapy program, it is advisable to perform plasmapheresis (plasma exchange) up to 1.5 – 2 liters. Performing plasmapheresis is indicated not only as a procedure aimed at preventing and treating tumor collapse syndrome, but also at correcting coagulation complications (DIC syndrome) [4, 5].

Conclusions. OPL should be considered as an urgent medical situation requiring the immediate appointment of ATRA (completely transretinoic acid) in combination with polychemotherapy against the background of accompanying treatment. Early treatment, timely diagnosis and absence of hyperleukocytosis at the onset determines the survival of patients. The induction treatment stage is complex and requires massive accompanying therapy, the remission consolidation stage is significantly less toxic and can be performed on an outpatient basis.

In cases of insufficient efficacy or intolerance of the drug ATRA, relapse of the disease, ATO (arsenic trioxide) is used to treat OPL. With gross violations of the maintenance therapy regime, the likelihood of relapse is very high. Modern protocols are more effective than previously used aggressive chemotherapeutic protocols and are less toxic for patients who have been diagnosed with OPL for the first time. The presented protocols have a very high therapeutic effect, with minor differences in the percentage of survival and mortality, as well as maintaining complete remission.

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