**ISSUES OF NEUROLEUKEMIA DURING THE LEUKEMIA IN ADULTS: TREATMENT AND PREVENTION.**

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One of the most dramatic issues of a hematologic decease is the problems of growth of leukemia cells and its severe complications, neuroleukemia is being of them.

Neuroleukemia (neuroleukemia, meningeal leukemia, leukemic meningitis) - is a metastatic lesion of the central and peripheral nervous systems, it is also a neurological complication of different forms of acute leukemia.

The first time the attack of the nervous system by leukemia was described in 1823, where the symptoms were described by headaches, vomiting, drowsiness or irritability, seizures and severe cases of coma.

Neuroleukemia may occur both during remission and the acute phase of the disease, it may occur sub clinically and lead to a subsequent relapse. According to A.I Vorobyov (1990), neuroleukemia is not a clinical condition, it is a cytosis [6]. According to S.V. Zholobova`s pathological studies (2009), there are two pathways of leukemic cells in the CNS: contact through the skull and bones of the spine to the dura mater and its funnel cranial and spinal nerves. This was proved by the frequency of involvement in the process of nerve trunks, primary localization of leukemia cells is in the membranes of the brain base in rigid sheath and stroma ternary nodes, pituitary membranes, combination leukemids on the scalp with the presence of leukemic infiltrates in the hard shell of the cranial vault and Usury skull. The second way of metastasis - is diapedesis - from overcrowded vessels soft shell in the cerebrospinal fluid and brain tissue by perivascular spaces [5].

Along the increasing the length of life of patients with leukemia incidence of neuroleukemia rises sharply. Thus, according to data of some authors among patients surviving the first year of neuroleukemia occurs in 26.8%; if the duration of life increased to 3 and 5 years, the frequency neuroleukemia was about 70.5% and 92.1% [3, 4]. The absence of clinical manifestations of neuroleukemia doesn`t mean the absence of leukemic remission of the shells. Thus, 50% of patients without clinical manifestations of neuroleukemia with normal cerebrospinal fluid at morphological study revealed leukemic infiltration of the brain membranes. In case of brain damage substances focal lesion on computed tomography or pathological focus on EEG can be detected [4].

Through the development and improvement of methods of diagnosis and treatment of leukemia in the beginnings of the twentieth century, the effectiveness of treatment and prevention of leukemia in Uzbekistan has substantially increased.

Practical help of Scientific Research Institute of Hematology and Ministry of Health in mastering the treatment technology and in the training of medical personnel by training of specialists in leading clinics, allowed to introduce modern protocols of treatment of leukemia, not only in the clinic of the Institute, but also in the regional centers of hematology. Despite the success, the problem of neuroleukemia in leukemia is far from complete. The protocol treatment does not exclude the possibility of recurrence and fatal secondary leukemia (also known as relapse).

The effectiveness of therapy in patients of different age groups are mixed. According to various statistics, only 10-30% of patients have a long life and relapse-free flow of leucosis.

An inadequate amount of diagnostic facilities in city and regional medical centers, the lack of qualified medical laboratory does not allow for adequate diagnosis with verification of all the nuances of diagnosis and factors of risk. Indiscriminate treatment for a variety of chemotherapeutic regimens without complying dose intensity and stages of primary therapy, which consequently increases the risk of neuroleukemia is still widely spread.

Since the 70's a program of total therapy of acute leukemia, providing carrying out preventive treatment and prevention neuroleukemia is being developed. However, currently there is no radical neuroleukemia prevention programs - the occurrence of the latter remains high, especially in patients - centenarians, in the presence of adverse projecting factors at the initial stage of leukemia [3.7].

Without the implementation of such practices, preventing the prevalence of neuroleukemia is decreased, but in over-all, it is 15%. Despite ongoing prevention neuroleukemia, the frequency of its occurrence is still high, especially in patients who live a long time. [6]

As it was stated above, it is obvious that preventive measures reduce the frequency of neuroleukemia, but the percentage of patients with lesions of the nervous system leukemia process is still high. We can say that the current usage of methods and means of preventing in different combinations and rhythms do not allow to achieve complete eradication of leukemia cells in the nervous system and, consequently, the occurrence neuroleukemia relegated to more prolonged terms. We need to search more effective measures for neuroleukemia prevention.

As preventive measures are not currently providing complete eradication of leukemic cells in the nervous system, the treatment neuroleukemia is an actual problem.

During conducting specific treatment, scientists recommend to assign detoxification and dehydration products (lasix, magnesium sulfate, 40% glucose solution), drugs to enhance the metabolic processes in the nervous system (acid glutamic, Aminalon), adaptogens (Eleutherococcus extract liquid) [6 ].

According to many researchers the effectiveness of this therapy is mainly determined by the localization of leukemic infiltration and treatment regimen, to a lesser extent - a form of acute leukemia. Therefore, before prescribing the treatment they recommend to conduct a neurological examination of the patients and determine the shape of neuroleukemia in order to make a determination of which departments should be mainly involved in the pathological process [7].

Attempts to supplement induction therapy for acute leukemia by means of preventing the development of neuroleukemia, have been carried out since the '60s. According to most researchers, the use of methotrexate in remission induction significantly reduces the occurrence of neuroleukemia [9]. However, subsequent observations have shown that even multiple intrathecal administration of methotrexate does not eliminate the risk of developing neuroleukemia. In this connection, in the "total" treatment, along with intrathecal methotrexate provided irradiation of the brain and spinal cord [10].

In present times, there is enough understanding of various hematological schools for using combined chemo and radiotherapy for the purpose of preventing neuroleukemia in adults. According to H. Hustu, radio therapy (with brain and spinal cord exposure to S3 level) in 207 patients at a dose of 2400 rad - over a three-year survival rate of 50% in patients without development neuroleukemia is achieved [12].

According to P. Pouillart, the best results were obtained with the combined use 10 mg/m of methotrexate and Cytosar 2-3 times a week with a cranium irradiation and spine at a dose 2400 rad. At indicated method of prophylaxis neuroleukemia was developed in 6.6% of cases, and in patients who did not receive prophylactic treatment (76 patients), - 34% of cases. Results shown by H. Lieven (1976), about performing craniospinal radiation show specific reductions in CNS to 5 - 7% with simultaneous increase in 5-year survival rate approximately 10 times instead of 50 - 70% for the group of patients on whom it not been performed[7].

B. Considine and others at the period of remission used single intrathecal administration of methotrexate at a dose of 0.5 mg / kg, once in 10 days from the radiation of cerebrum (120 rad. in 2 days) and spinal cords (70 rad). Complete remission was observed for 3 years in 72 patients with the comparison group [7].

Neuroleukemia prevention should be started early - in the period of induction therapy. Many foreign hematologists prefer combined methods of including cranial radiation to a total dose of 18-24 Gr and endoluminal administration of methotrexate 12.5 mg\m2 4-6 times at intervals of 3-5 days, also combination of methotrexate and cytosar (30 mg\m2) [11 ,12]. The test, confirming the diagnosis, is the study of cerebrospinal fluid, ocular fundus, EEG, adherence of neurological symptoms for treatment - the most versatile means is intrathecal methotrexate at a dose of 12.5 mg\m2 every 5 days. [12]

Besides methotrexate many local and foreign authors recommend administration of other cytotoxic drugs: cytosar (30 mg\m2), cyclophosphamide (80-100 mg\m2). In case of insufficient effects, it is advisable to use radiation therapy in the local single dose of 50-200 Gr in 1-2 days, the course is continued until a clinical effect is achieved. Neuroleukemia treatment should be continued until the complete rehabilitation of cerebrospinal fluid [7.12].

Poor prognosis of treatment of adult patients with isolated neuroleukemia explains the continued interest of specialists to this problem: a four-year overall survival among adults is only 6% [4].

The necessity neuroleukemia prevention in adult patients has been proven by various foreign multicenter randomized trial [4,7]. In comparison, the results of treatment of two groups of patients with acute lymphoblastic leukemia: one prevention of neuroleukemia included cranial irradiation (24 Gr) and intrathecal methotrexate; in another patients were excluded from therapy. The following results were obtained during the study: 10.7% in the first group, the frequency of CNS, in the second (without prophylaxis of neuroleukemia). This rate was significantly higher and reached 35.29%. The difference between the disease-free and overall survival in the study groups was not found.

Similar results were obtained by Russian scientists during the retrospective analysis of treatment outcomes of 248 patients (from 1969 to 1983), where the CNS has developed in 32% of patients among those patients who did not carry out preventive maintenance. In the group of patients whose treatment included neuroleukemia prevention, the rate was 12.5% [7].

Practice shows that the occurrence of neuroleukemia varies in different groups of patients. Adverse factors are considered to be a high level of lactate dehydrogenase of serum (> 600 U/L) and high proliferative index (S + G2M> / = 14%): where throughout the year neuroleukemia is developed in 55% of patients, and in patients with normal indicator it is 4% [8].

If advisability of neuroleukemia prevention is currently recognized as an integral part of treatment of acute lymphoblastic leukemia [7], the question of choosing strategy and tactics of its preventive therapy, determination of "gold standard" in hematology is still open.

There are several basic options of neuroleukemia prevention. The first - intrathecal therapy, which effectively prevents the occurrence of neuroleukemia in patients with leukemia at standard risk of relapse. According to some reports, intrathecal methotrexate in adult patients, the incidence of neuroleukemia is 8-19% [4.7]. Triple intrathecal therapy (TIT) provides good results in adult patients. The most effective one in the standard-risk group, while in the high-risk group, even in combination with high-dose have a high incidence of neuroleukemia [12].

The second option is neuroleukemia prevention - a combination of intrathecal therapy and systemic high-dose chemotherapy, which is effective in adult patients with acute lymphoblastic leukemia (neuroleukemia frequency - 3-12% [10,11]). This option is also effective in patients, exception of patients with initially high leukocytosis. After the failure of cranial irradiation in this group of patients with a high frequency neuroleukemia it was awarded - up to 26%, despite the wire intrathecal and intensive systemic therapy [11].

The third option, the efficacy of which is confirmed by numerous studies – connection of cranial irradiation (18-24 Gr) to intrathecal therapy. Frequency of neuroleukemia after the implementation of this variant of prevention is 4,7-16,1% [7].

During the radiotherapy scientists recommend to carry out both during stimulation and after consolidation. It should be noted that in patients with standard-risk transfer of radiation from the second month of therapy at a later date and replacement with high-dose therapy at high risk with the simultaneous introduction of triple intrathecal therapy during consolidation, re-induction and maintenance therapy were accompanied by increasing the frequency of CNS and the deterioration of the general results [ 12].

Thus, the most important principle of treatment and prevention neuroleukemia is the principle of differentiation, which required in choosing the mode of treatment and prevention to take into account the presence of the risk factors of the patient relapse.

**SUMMARY**

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One of the most dramatic concerns of hematology are teething problems in leukemia and its severe complications, one of which is neuroleukemia. It is evident that with increasing duration of life of patients with leukemia occurrence rises sharply in neuroleukemia. As a result, according to the data of some researchers, the number of patients who survived 1 year, neuroleukemia rose in 26.8%; if the duration of life increased to 3 and 5 years, the frequency neuroleukemia was 70.5% and 92.1% respectively. The most important standard of choosing the treatment and prevention in all of the cases are the principles of risk factors patients have to undergo with having the minimal chances of relapse.

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