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New opportunities in the treatment of chronic lymphocytic leukemia

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Abstract. Chronic lymphocytic leukemia (CLL) – the most common subtype of hemoblastoses (22–30%). It can have aggressive or indolent course, with diverse clinical symptoms. The foundation of this diversity is the molecular features of the disease. The incidence of CLL in Russia is 6.67 per 100 000 population. By 2016 several novel therapies for CLL have been registered in Russia, including ibrutinib and obinutuzumab, but the implementation of the novel drugs into daily practice meets certain difficulties. This article describes some of them based on the experience on the N.A.Semashko Nizhny Novgorod regional clinical hospital.

Keywords: chronic lymphocytic leukemia, ibrutinib, obinutuzumab.

Chronic lymphocytic leukemia (CLL) is the most common type of hemoblastosis (22–30%). In 2013, 3851 cases of CLL were registered in the Russian Federation, in 2014 - 3962 cases; the incidence in 2014 was 6.67 per 100 thousand people. Among patients with CLL, 54.8% are elderly people over 65 years old. About 40% of patients have a slowly progressive course of CLL and do not require therapy at the time of diagnosis [1, 3].

Speaking about the features of CLL, it should be noted that this is a large group of patients, heterogeneous in the approaches to management used, depending on age, comorbidity and prognostic factors. Features of CLL determine the individualization of the approach to each patient on the part of the outpatient and inpatient doctor. A distinctive feature of CLL is that the detected disease sometimes does not require treatment: without confirmation of progression, therapy in these patients does not begin [2,6,8].

Currently, in real clinical practice, a doctor has to deal with diverse problems: clinical, diagnostic, organizational and methodological, administrative and financial, issues of adherence to therapy and improving the quality of life.

Clinical problems include the definition of groups of patients in whom the use of certain regimens and drugs is preferable, individual selection of therapy for a particular patient, taking into account the patient's comorbidity, drug tolerance, complications of the underlying disease and therapy [4, 5].

New diagnostic difficulties arise. With the introduction of new drugs into practice, doctors will have to apply concepts such as minimal residual disease, achievement of molecular remission in CLL, which increases the burden on laboratories, which must be expanded and modified.

Following this, organizational and methodological problems arise, such as an increase in the observed group of patients, observation by related specialists, outpatient management of patients and their education, adherence to therapy [8,11].

Adverse events with ibrutinib

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With ibrutinib, various types of adverse events occur: hematological, non-hematological, leukocytosis with lymphocytosis.

If you compare them with the adverse events of the BR and FCR protocols, it becomes obvious that the toxicity of these drugs is much higher.

Most of the adverse events refer to the 1st or 2nd degree, they do not require hospitalization and medical correction. At the same time, it is characteristic for ibrutinib that the longer the patient uses this drug, the fewer undesirable phenomena occur - the toxicity goes away with the intake of this drug. In particular, the hematological toxicity of therapy decreases with continued administration of drugs - there is a sustained increase in hemoglobin levels in patients with anemia (84% on ibrutinib vs 45% on chlorambucil, $p < 0.0001$), platelet count in patients with thrombocytopenia (77% on ibrutinib vs 43% on chlorambucil, $p = 0.0054$) [9, 12].

In the practice of the hematology department of the N.N. N.A. Semashko observed neutropenia of the 2nd and 3rd degree, which did not lead to the cancellation of ibrutinib.

Atrial fibrillation, which develops with the use of ibrutinib, occurs with a frequency of 6-10%. The exact mechanism of its development is unknown. Presumably, this is due to the suppression of the activity of the PI3K-AKT signaling pathway, which is involved in the maintenance of normal electrical function of the atria. With regard to this negative phenomenon, it is worth considering the fact that patients are elderly people, who are initially very likely to have cardiological pathology: coronary heart disease, postinfarction and atherosclerotic cardiosclerosis, rhythm disturbances. All this is not an absolute contraindication for the use of ibrutinib [10, 14].

In the hematology department of the N.N. N.A. Semashko is currently observing patients with atrial fibrillation. These patients need more regular monitoring: consultations with a cardiologist, electrocardiography (ECG), ECG monitoring, echocardioscopy, control of drug intake for cardiac pathology. However, this is not an insoluble problem from an organizational point of view and an indication for discontinuation of ibrutinib - from a clinical one. However, if atrial fibrillation persists, consideration should be given to continuing with ibrutinib or adjusting the dose [13, 15].

Negative hemorrhagic manifestations are also characteristic of ibrutinib. In the Resonate and PCYC-1102 studies, grade 1 petechiae and bruising were the most common (13% and 20% in PCYC-1102 and 13 and 11% in the ibrutinib group in the RESONATE study, respectively); There were no reports of grade 4-5 hemorrhagic manifestations. Most of the hemorrhagic manifestations were observed during the first 3–6 months of therapy and did not require additional intervention. Treatment was discontinued due to severe hemorrhages in 1% (4/327) of patients .

lymphocytosis

Lymphocytosis occurs in patients simultaneously with a decrease in the size of the lymph nodes and spleen and with a decrease in the degree of cytopenia. The

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average duration of lymphocytosis in patients with CLL is usually 18.7 weeks. Lymphocytosis resolved in 77% of patients with CLL (mean follow-up 9.4 months). Temporary isolated lymphocytosis while using ibrutinib is not a reason to interrupt therapy. The main problem for the hematology department of the Nizhny Novgorod OKB im. N.A. Semashko began to assess the response to the occurrence of lymphocytosis after the use of ibrutinib. An additional study was used for the assessment - multislice computed tomography (MSCT). The answer was based on the contraction of lymph nodes, and not on lymphocytosis.

All the undesirable effects that we observed with ibrutinib are probably related to the fact that patients who used this drug received it in the 3-4th line of therapy. None of the negative events we observed were an unsolvable problem limiting specialists in the use of ibrutinib for the treatment of CLL.

Adverse events with obinutuzumab The main adverse events observed with obinutuzumab are infusion reactions, especially with the first administration. Therefore, a very strict adherence to the instructions, strict use of premedication when using the drug, monitoring the patient's condition are necessary. However, infusion reactions were rare with subsequent administrations of obinutuzumab.

Potential risk factors for obinutuzumab include: high baseline lymphocyte count, pretreatment splenomegaly, lymph node volume, comorbidities of the respiratory system, neutropenia before treatment.

Of all these risk factors, the most important, in our opinion, is the tumor volume at which obinutuzumab is administered. Tumor lysis is so rapid that it becomes a more severe problem than an infusion response that can be controlled. Therefore, when using obinutuzumab, prevention of tumor lysis syndrome is very important.

clinical researches

Over the past 6 years, 134 patients have been included in clinical trials in the hematology departments of the Bukhara Regional Multidisciplinary Medical Center. Clinical research has become firmly established in clinical practice with both positive and negative aspects. The following should be considered as positive: new highly effective drugs; strict adherence to protocol procedures - transfer of experience into practice; obtaining information on research results; the effectiveness of the treatment. The negative include: selection of patients; limiting the use of the experience of treatment with new drugs in real practice.

Conclusion

The introduction of new drugs into clinical practice is associated with many difficulties, among which clinical (adverse events) constitute a smaller part than administrative and financial ones. To solve these problems, it is necessary to solve such problems as the creation and improvement of the register of lymphoproliferative diseases; monitoring the availability and frequency of use of modern diagnostic and treatment methods; determination of the real need for medical technologies and medicines; strengthening the interaction of the professional medical community and

healthcare organizers at the regional level on the availability of treatment; expansion of interaction between federal centers and regional clinics in order to provide expert support for the introduction of new treatment technologies into practice; introduction of modern diagnostic methods; introduction of treatment and rehabilitation of diseases based on advanced technologies; expansion of the types of high-tech medical care based on the procedures for the provision of medical care.

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