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NEW APPROACHES IN DIAGNOSIS AND TREATMENT OF CHRONIC MYELOID LEUKEMIA: FOCUS ON TARGETED THERAPY

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Introduction

Abstact. The development of malignant tumor diseases of the blood system is associated with the occurrence of a number of successive gene mutations leading to the development of a malignant cell clone. It is also known that during therapy, the primary population of malignant cells can acquire secondary mutations, changing under the influence of various selection factors in the patient's body (immunological selection, the action of cytostatic drugs, etc.). These malignant subclones with combinations of gene mutations can subsequently lead to relapses of the disease. The diversity of gene pathology in the patient's body significantly affects the prognosis and treatment outcomes of patients with leukemia and lymphoma. To assess the clinical risk in each specific case, a detailed description of genetic aberrations is required, and this requires determining the nucleotide sequence of the target gene in malignant cells. Modern molecular diagnostics for leukemia is based on the detection of specific gene mutations characteristic of a particular type of leukemia. The main method is molecular genetic diagnostics based on polymerase chain reaction (PCR) with analysis of target gene regions, which is carried out in the laboratories of large oncohematology clinics. Chronic myeloid leukemia (CML) is a malignant hematological disease characterized by uncontrolled proliferation of myeloid cells. The main pathogenic mechanism is the presence of a specific chromosomal abnormality - the Philadelphia chromosome, which leads to the formation of the oncogenic protein BCR-ABL with tyrosine kinase activity. In recent years, approaches to the diagnosis and treatment of CML have evolved significantly due to the introduction of targeted therapy and advances in molecular genetic diagnostics [1].

Target

The aim of this article is to evaluate the effectiveness of modern targeted treatments for chronic myeloid leukemia (CML) and to study the prospects for using new diagnostic methods for early detection and monitoring of the disease.

Diagnosis of CML

Traditional methods for diagnosing CML include bone marrow and peripheral blood morphology, cytogenetic analysis for the Philadelphia chromosome, and fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) to detect the BCR-ABL transcript. However, with advances in technology, diagnostics have become more accurate and accessible. The introduction

of digital PCR (ddPCR) and next-generation sequencing (NGS) has allowed more sensitive detection of minimal residual disease (MRD), which is critical for monitoring the effectiveness of therapy [2,3].

Currently, a large number of gene and chromosomal mutations observed in chronic leukemia have been identified. Thus, based on these data, a detailed molecular classification of acute myeloid leukemia (AML) is already possible [4]. In a multicenter study, the authors studied the sequence of 111 genes in 1,540 patients after induction chemotherapy. Using cytogenetic analysis and deep DNA sequencing, so-called driver mutations, i.e. gene abnormalities associated with the development of AML, were identified. These included fusion genes, other oncogenic mutations, and chromosome ploidy abnormalities. A total of 5,234 different mutations in 76 genes were detected. At least 2 mutations were found in 86% of patients. The most frequently detected aberrations were genes FLT3, NPM1, DNMT3A, NRAS. NPM1 mutations usually arose later, which reflects their role in the further evolution of leukemic transformation. At the same time, joint mutations, for example, NPM1 and NRASG12/13, as well as combined mutations of the FLT3 gene, were observed relatively often. Eleven subgroups, or classes, of AML were distinguished based on the functional parameters of the genes involved. The most common AML cases were with NPM1 mutations (27%). The second most frequent subgroup included clinical cases with mutations in genes encoding splicing (structural rearrangements) of RNA molecules, chromatin state, or RNA transcription. TP53 mutations with complex chromosomal aberrations were detected in 13% of patients, which made it possible to distinguish them into a special pathogenetic group. Although the possibilities of clonal mutation analysis were limited, mutations in the genes encoding epigenetic proteins (DNTM3A, ASXL1, IDH1/2, TET2) were detected earliest. All these heterogeneous molecular genetic data were compared with the clinical picture and outcomes of the disease. It was found, for example, that an unfavorable outcome was more often observed in groups with mutations in genes regulating nuclear chromatin functions and RNA transcription. Another high-risk group were patients with TP53 gene mutations and complex karyotype abnormalities. These molecular criteria will certainly confirm the provisions of the current AML classification and will allow better prediction of individual risk for patients [5].

Targeted therapy

Targeted therapy is able to stop the proliferation and spread of tumor cells by affecting the molecules involved in tumor growth and progression. Molecular targeted therapy is considered specific for certain types of tumor cells and is more effective than chemotherapy and radiotherapy, being less toxic to normal cells. At the same time, targeted therapy drugs can be combined with each other and with standard chemotherapy to provide a systemic effect on tumor cells, which ultimately increases the life expectancy of patients and improves its quality. The stage of the disease is not a limiting factor for targeted therapy. In fact, targeted therapy, pathogenetic in nature, is aimed at affecting intracellular signaling pathways, gene expression and surface cell receptors that ensure the maintenance of the fundamental properties of tumor cells responsible for their emergence, proliferation and spread in the patient's body, maintaining the viability of these cells under standard chemotherapy, i.e. for the response of cells to damaging effects. Numerous drugs of targeted therapy are constantly included in Russian-language reference manuals on drug therapy of tumors [6], not to mention English-language ones. Targeted methods also include such common approaches as 16S sequencing, sequencing of genes encoding immune response molecules, in particular HLA typing, and many other applications. Ultra-deep targeted sequencing also allows analyzing substitutions and small insertions/deletions in cell clones (at a frequency of up to 1% in the cell population). Detection of multiple nucleotide substitutions, deletions and other aberrations in stem cells of patients with oncohematological profile is becoming increasingly common. In the last 5-6 years, with the advent of technological platforms and devices for NGS, the tasks of simultaneous analysis of multiple genes have become not only feasible, but also quite cost-effective.A revolutionary breakthrough in the treatment of CML was the discovery of tyrosine kinase inhibitors (TKIs) that block the activity of the BCR-ABL protein. The first drug in this

class, imatinib, significantly improved the prognosis of CML patients, allowing most of them to achieve long-term remission. Subsequently, more potent second- and third-generation TKIs, such as dasatinib, nilotinib, and bosutinib, were developed to treat cases of imatinib resistance or BCR-ABL mutations [7].

Studies have shown that the use of TKIs resulted in 5-year patient survival rates exceeding 90%. However, managing TKI resistance and side effects remains challenging as these factors may limit the long-term use of the drugs.Radioimmunotherapy (or targeted radionuclide therapy) is a type of targeted therapy that uses monoclonal antibodies labeled with a radionuclide directed against tumor-associated antigens. The radionuclides most commonly used in radioimmunotherapy are those that emit β- and α-radiation. Preclinical studies have tested 225 Ac conjugated to PSMA-617 (prostate-specific membrane antigen) compounds for prostate cancer therapy; lintuzumab conjugated to 213 Bi, 225 Ac, and 227 Th for myeloid leukemia therapy; 212PB-TCMC-conjugated 22 monoclonal antibodies in ovarian cancer xenografts. The following drugs have been tested in clinical trials: [213 Bi]-DOTATOC in patients with progressive neuroendocrine tumors; [213 Bi]-DOTA-substance P for the treatment of patients with recurrent glioblastoma; 177Lu-labeled PSMA-617 in the treatment of metastatic castration-resistant prostate cancer; omburtamab conjugated with 131I in patients with neuroblastoma. Registered drugs for radioimmunotherapy include 90Y-labeled anti-CD20 antibody ibritumomabtiuxetan (Zevalin®), 131I-labeled anti-CD20 antibody tositumomab (Bexxar®), and 177Lu-DOTATATE (Lutathera®). The combination of targeted radionuclide therapy with other antitumor drugs to achieve a synergistic antitumor effect deserves attention, for example, the drug [212Pb]DOTA-MTATE with 5-fluorouracil; the drug [212Pb]-trastuzumab with gemcitabine and paclitaxel. Currently, the potential is being created for targeted radionuclide therapy to complement existing forms of malignant neoplasm therapy and improve treatment options and quality of life for patients with highly resistant tumors and late stages of oncological diseases. However, due to the high cost of targeted drugs, radiopharmaceuticals and generators, new developments in this area are difficult, which makes further research in this direction relevant [8,9,10].

Resistance management and new therapeutic strategies

Resistance to TKIs can arise from mutations in the BCR-ABL gene that alter the structure of the tyrosine kinase, making it insensitive to inhibitors. To address this issue, current research is focused on developing new TKIs that can inhibit mutant forms of the protein. One promising drug is ponatinib, which has shown efficacy against the T315I mutation, one of the most difficult to treat forms.

Additionally, studies are investigating the use of combination therapy using TKIs and immunomodulators, as well as the potential of gene therapy using CRISPR technology to correct mutations [10].

The Future of Targeted Therapy and New Approaches

In recent years, attention has shifted to the possibility of stopping therapy in patients who have achieved a profound molecular response. This strategy, known as treatment-free remission (TFR), is being actively studied in clinical trials. Preliminary data suggest that about 40-60% of patients can maintain remission without ongoing therapy, reducing the risks of side effects and improving quality of life.

New diagnostic techniques such as liquid biopsy are also gaining attention. These techniques allow highly sensitive detection of molecular markers and minimal residual disease without the need for invasive procedures.

Programmed polychemotherapy (PCT) (protocols AIEOP AML, COG AAML, NOPHO AML,

AML BFM, St Jude AML), based on a risk-adapted approach to treatment, allows to achieve overall survival (OS) in 65-70% of patients. Such results were possible due to stratification of patients into prognostic risk groups, improvement of accompanying and chemotherapeutic treatment. Nevertheless, the high frequency of AML relapses, reaching 35%, predetermines the need to search for new ways of therapeutic action on tumor cells [1, 2]. The study of the molecular basis of leukemogenesis made it possible to determine the targets of antitumor action. H. Bolouri et al. In 2018, the results of the TARGET (Therapeutically Applicable Research to Generate Effective Treatments) study of the Children's Oncology Group – National Cancer Institute (COGNCI) cooperative group were published. The goal of the study was to clarify the transcriptional, mutational, and epigenetic "portrait" of AML in children. Using whole-genome sequencing techniques and gene methylation profiling, it was possible to identify a number of chimeric transcripts, focal deletions, and recurrent mutations unique to AML in a pediatric cohort of patients, with some of the identified aberrations clearly associated with a worse prognosis. In particular, the most common mutated genes in childhood AML are RAS, KIT, and FLT3. In addition, new FLT3 mutations specific to pediatric AML were identified. In contrast, mutations in the DNMT3A, IDH1, and IDH2 genes were found to be present in a minority of cases. Chimeric genes have been identified that are predominantly or exclusively found in childhood AML: CBFA2T3-GLIS2 and NUP98-NSD1. A detailed study of the biological specificity of childhood AML opens up many therapeutic application points [11].

BCL-2 protein Venetoclax is a targeted antitumor agent belonging to the class of so-called BH3-mimetics. Drugs in this category inhibit antiapoptotic molecules such as BCL-2, BCL-w and BCL-XL. By specifically binding to the target, venetoclax copies the action of physiological BCL-2 antagonists, which leads to the inclusion of programmed cell death mechanisms through the activation of proapoptotic proteins (such as BIM) and the caspase cascade. The study by SE Karol et al. (NCT03194932) demonstrates the role of safety and efficacy of venetoclax in combination with high-dose cytarabine in children with relapsed and refractory forms of AML. All patients received venetoclax 240–360 mg/m2 on days 1–28 of treatment, high-dose cytarabine (1000 mg/m2 every 12 hours, 8 doses), or low-dose cytarabine (100 mg/m2 every 12 hours, 20 doses). If the previously received total dose of anthracyclines was < 270 mg/m2 equivalent to doxorubicin, idarubicin 12 mg/m2 was added to the treatment program on day 8 [12].

Conclusion

Chronic myeloid leukemia has transformed from a fatal disease to a manageable condition due to the introduction of targeted therapy using tyrosine kinase inhibitors. Modern diagnostic methods such as next-generation sequencing and digital PCR allow for more effective monitoring and better prediction of treatment resistance. The future of CML treatment lies in the development of combination therapies, gene editing technologies, and improved diagnostic methods such as liquid biopsy, which will further improve patient outcomes.Revolutionary NGS technologies in recent years have increased the reliability and reduced the cost of deep sequencing of genomic sequences, accelerated gene diagnostics, and expanded the applications of genomic sequencing. In the future, we can expect the use of NGS methods for the analysis of minimal DNA samples, for example, in single cells or cell-free DNA in blood plasma. However, the widespread use of NGS methods in clinical practice requires the improvement of computer technologies for the full processing of large databases obtained in different laboratories, the development of standardized and reproducible bioinformatics methods suitable for the differential diagnosis of leukemia and typing of histocompatibility antigens.

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