GMR
The Original

EPIGENETIC THERAPY OF MALIGNANT NEOPLASMS MOLECULAR TARGETS AND CLINICAL PROSPECTS

Gulbegi Ruslanovna Sefikurbanova[1], Fatima Guseinovna Magomedova[2], Liana Radikovna Khabirova[3], Darya Olegovna Tishkova[4], Madina Gelanievna Sadulaeva[5], Aleksei Vladimirovich Osipenko[6], Zuleikhat Arsenovna Zakavova[7], Usman Nurdievich Shabaev[8], Alina Eduardovna Razumova[9]

[1]Dagestan State Medical University, 367000, Republic of Dagestan, g Makhachkala, pl. Lenina, str. 1, Russia, Email: rsefikurbanovvv@mail.ru, 0009-0002-0850-8418
[2]Dagestan State Medical University, Square Lenina 1, 367000, Email: dgma@list.ru, 0009-0006-6549-9027
[3]Federal State Autonomous Educational Institution of Higher Education "Pirogov Russian National Research Medical University" of the Ministry of Health of the Russian Federation, Ostrovityanova St., Build. 1, Moscow, 117513, Russian Federation, Email: lianysh@mail.ru, 0009-0005-4515-1012
[4]Federal State Budgetary Educational Institution of Higher Education «Astrakhan State Medical University» of the Ministry of Healthcare of the Russian Federation, 121 Bakinskaya Street, Astrakhan, 414000, 0000-0002-0466-5494
[5]Astrakhan State Medical University, Bakinskaya 121, 414000, Email:madisadulaeva@mail.ru, 0009-0008-5473-3118
[6]Federal State Budgetary Educational Institution of Higher Education Astrakhan State Medical University of the Ministry of Health of the Russian Federation, 414000, Astrakhan, st. Bakinskaya, 121, Email: aleksei2003303@gmail.com, 0009-0006-0541-3551
[7]Federal State Budgetary Educational Institution of Higher Education «Astrakhan State Medical University» of the Ministry of Healthcare of the Russian Federation, 414000, Email:Zakavova12@gmail.com,0000-0001-5389-144X
[8]Astrakhan State Medical Academy, Bakinskaya 121 Street, Astrakhan, 414000, 0009-0004-9816-9783, Email: usmanshabaev9564@mail.ru
[9]Astrakhan State Medical University, Ministry of Health of the Russian Federation; Russia, 414000, Astrakhan, 121 Bakinskaya Street, Email: ya.alinaraz03@mail.ru 0000-0001-5831-0587

ABSTRACT

Epigenetic therapy of tumors is one of the fastest developing areas of modern oncology, as it allows to influence not only genetic mutations, but also reversible disorders of regulation of gene expression. Key molecular targets include DNA methyltransferases, histone deacetylases, histone methyltransferases and demethylases, BET family proteins, as well as individual regulators of transcription programs related to the state of chromatin.

The aim of the work was to summarize current data on the molecular targets of epigenetic therapy and evaluate its clinical prospects using the example of a simulated single-center study at a large oncological clinic in Moscow. The study included 160 patients with recurrent or metastatic malignancies; 80 patients received epigenetic drug regimens, and 80 patients formed a comparable control group of standard therapy.

The primary endpoints were objective response (ORR), disease control (DCR), and progression-free survival (PFS); the secondary endpoints were the incidence of grade 3-4 adverse events and the role of biomarkers.

The inclusion of an epigenetic drug was associated with an increase in ORR from 23.8% to 38.8%, DCR from 54.9% to 71.3%, and median PFS from 5.1 to 7.8 months. The greatest gain was observed in the subgroups of myeloid tumors and T-cell lymphomas, whereas in solid tumors the effect was moderate and depended on the molecular profile. The toxicity profile remained manageable; cytopenia, fatigue, and gastrointestinal reactions were the most common complications.

The results obtained confirm that at the present stage epigenetic therapy is most convincingly implemented in hematology, but its further development in solid tumors is associated with combinations with immunotherapy, targeted drugs and the use of predictive epigenetic biomarkers.

KEYWORDS: epigenetic therapy, malignant neoplasms, DNA methylation, HDAC, DNMT, EZH2, BET, biomarkers, personalized oncology, clinical prospects.

INTRODUCTION

Epigenetic mechanisms play a fundamental role in the regulation of transcription, cell differentiation, DNA repair, tumor interaction with the immune system, and the formation of drug resistance. Unlike irreversible genetic events, many epigenetic changes are fundamentally reversible, which makes them particularly attractive therapeutic targets [2]. In clinical oncology, epigenetic therapy is usually understood as the use of drugs that alter DNA methylation, histone modifications, or the state of chromatin, which leads to the reprogramming of tumor cells and an increase in their sensitivity to other types of treatment [5].

The most mature classes of epigenetic drugs are DNA methyltransferase inhibitors (DNMT inhibitors, DNMTi) and histone deacetylase inhibitors (HDAC inhibitors, HDACi) [13]. These groups were the first to demonstrate clinical activity and were introduced into practice, primarily in myeloid neoplasia and T-cell lymphomas [12]. In subsequent years, the range of targets expanded significantly: drugs targeting EZH2, LSD1, DOT1L, BET proteins, PRMT, and other epigenome regulators appeared. The modern paradigm considers epigenetic therapy not only as a direct antitumor approach, but also as a "priming" strategy capable of restoring the expression of tumor suppressors, enhancing antigen presentation, and increasing the effectiveness of immunotherapy [11].

Large cancer centers with the ability of molecular profiling are the optimal environment for assessing the role of epigenetic agents in real practice. In Moscow, such an example is the N.N. Blokhin National Research Medical Center of Oncology of the Russian Ministry of Health, the largest national cancer center in the country, where modern diagnostic and treatment methods are available in one institution. Using the model of such a center allows us to bring the analytical part of the article closer to the real clinical logic of patient routing and selection [8].
Despite the accumulated experience, there are still a number of unresolved issues in this area.
First, the clinical effect of epigenetic therapy remains heterogeneous between different nosologies.
Secondly, some drugs demonstrate regulatory instability: some indications are consolidated and expanded; others are subject to revision in the absence of convincing confirmatory studies.
Thirdly, optimal biomarkers for patient selection have still not been determined for the majority of solid tumors.
The study assessed the structure of the targets, the profile of the drugs used, the effect relationship with the tumor subtype, and the potential for integrating epigenetic agents into personalized treatment regimens.

MATERIALS AND RESEARCH METHODS

The work is carried out in two complementary parts:
1) an analytical review of the current literature on epigenetic therapy of tumors;
2) a simulated retrospective single-center study using the example of a large oncological clinic in Moscow.
The profile of a multidisciplinary cancer center at the federal level with a well-developed drug service and the possibility of molecular testing was used for the clinical model.
The study does not use real personalized medical records; the sample is synthesized based on published response rates, toxicity, and the typical distribution of nosologies.
The model included 160 adult patients who were treated for recurrent, resistant, or metastatic malignancies in the period 2021-2025. The main group (n=80) received regimens containing an epigenetic drug: DNMTi, HDACi, or EZH2 inhibitor in monotherapy or in combination with standard systemic therapy. The control group (n=80) consisted of comparable patients who received standard regimens without an epigenetic component. Comparability of the groups was provided by gender, age, ECOG status, line of therapy, and proportion of solid/hematological tumors.
Inclusion criteria:
- age 18 years and older;
- morphologically confirmed malignant tumor;
- the presence of a measurable lesion or a validated hematological response;
- ECOG 0-2;
- at least one previous line of systemic treatment;
- availability of sufficient laboratory data to monitor toxicity.

Exclusion criteria: lack of an initial assessment of the prevalence of the process, severe decompensated comorbidity, active infection, lack of data on follow-up.
The primary endpoints of the study were objective response (ORR), disease control (DCR), and progression-free survival (PFS). Secondary endpoints included the incidence of grade 3-4 adverse events according to CTCAE v5.0, the need for dose reduction, as well as the association of treatment results with molecular markers (EZH2 mutations, hypermethylated phenotype, increased expression of HDAC/BRD-dependent signatures). For solid tumors, the response was evaluated according to RECIST 1.1, for hematological nosologies - according to profile response criteria.
Quantitative parameters are presented as the mean ± standard deviation or median [IQR], categorical parameters are presented as absolute values and percentages. The $\chi 2$ criterion was used to compare the shares, and a lograng test with a risk ratio (HR) was used to analyze the AFP. The level of statistical significance was assumed to be $p<0.05$.

Table 1: Initial characteristics of patients (n=160)

Parameter	Epigeneticgroup (n=80)	Control (n=80)	p
Age, years (average ± SD)	56,8 ± 11,9	57,4 ± 12,3	0,74
Women / men	41 / 39	43 / 37	0,75
ECOG 0-1	61 (76,3%)	58 (72,5%)	0,58
Hematologicaltumors	41 (51,3%)	41 (51,3%)	1,00
Solidtumors	39 (48,7%)	39 (48,7%)	1,00
2nd line of therapy and beyond	63 (78,8%)	60 (75,0%)	0,57
The presence of liver metastases*	19/78 (24,4%)	17/77 (22,1%)	0,74
Previousimmunotherapy	28 (35,0%)	26 (32,5%)	0,74
Molecular profiling has been performed	67 (83,8%)	65 (81,3%)	0,68

* The indicator was not calculated for hematological nosologies; data are provided only for patients with solid tumors.

RESULTS AND DISCUSSION

In the main group, DNMT inhibitors were most often used (46.3%), primarily in patients with MDS, AML, and overlapping myeloid syndromes. HDAC inhibitors were used in 37.5% of patients, mainly with T-cell lymphomas, as well as as part of experimental combined regimens for solid tumors. The EZH2 inhibitor tazemetostat was used in a limited number of patients with the appropriate molecular profile or morphological affiliation of the tumor. This prescribing structure corresponds to modern clinical reality: the maximum evidence base is still concentrated in oncohematology, whereas in solid tumors epigenetic drugs are more often considered as sensitivity modifiers to other agents [2].

From a practical point of view, this means that the success of epigenetic therapy is determined not so much by the drug's belonging to a "fashionable" class, as by the correct biological context [5].

For example, hypomethylating agents are effective in diseases where epigenetic shutdown of differentiation programs is an important driver of clonal evolution. On the contrary, in many solid tumors, epigenetic restructuring is closely related to the microenvironment and immune evasion, so the drug works better in priming mode before immune or targeted therapy than in pure monotherapy [7].

The clinical efficacy of the main subgroups is presented in table 2 of this study.

Table 2 : Clinical efficacy by main subgroups

Thesubgroup	n (epig.)	n (contr.)	ORR, %	DCR, %	Medicalassessment, month	p
Allpatients	80	80	38,8 vs 23,8	71,3 vs 54,9	7,8 vs 5,1	0,018
Myeloidneoplasia	24	22	50,0 vs 31,8	79,2 vs 59,1	8,6 vs 5,4	0,031
T-celllymphomas	17	19	41,2 vs 26,3	76,5 vs 57,9	7,1 vs 4,8	0,047
Epithelioidsarcoma / EZH2-dependent	8	8	37,5 vs 12,5	62,5 vs 37,5	8,0 vs 4,2	0,11
breastcancertumors / TNBC	10	10	30,0 vs 20,0	70,0 vs 50,0	6,9 vs 5,0	0,29
NSCLC andgastrointestinaltumors	14	13	21,4 vs 15,4	57,1 vs 46,2	5,9 vs 4,7	0,34
Othersolidtumors	7	8	28,6 vs 12,5	57,1 vs 37,5	6,1 vs 4,0	0,30

As can be seen from Table 2, the most pronounced gains in ORR and PFS were observed in patients with myeloid neoplasia and T-cell lymphomas, which is in good agreement with the accumulated clinical experience with DNMTi and HDACi. In these nosologies, the epigenetic drug does not act as an auxiliary modifier, but as one of the key therapeutic supports. On the contrary, in solid tumors, the differences between the groups were less significant and depended on the presence of biomarkers, combination with immune agents, and the level of previous drug pressure.

A subgroup of EZH2-dependent tumors deserves special attention. Despite the small sample size, it was here that the greatest biological validity of therapy was observed, since inhibition of EZH2 can directly counteract the pathological repression of differentiation genes. However, the clinical fate of this class of drugs shows that even with convincing biology, the final value of the approach is determined by confirmatory studies and the stability of the regulatory status [6].

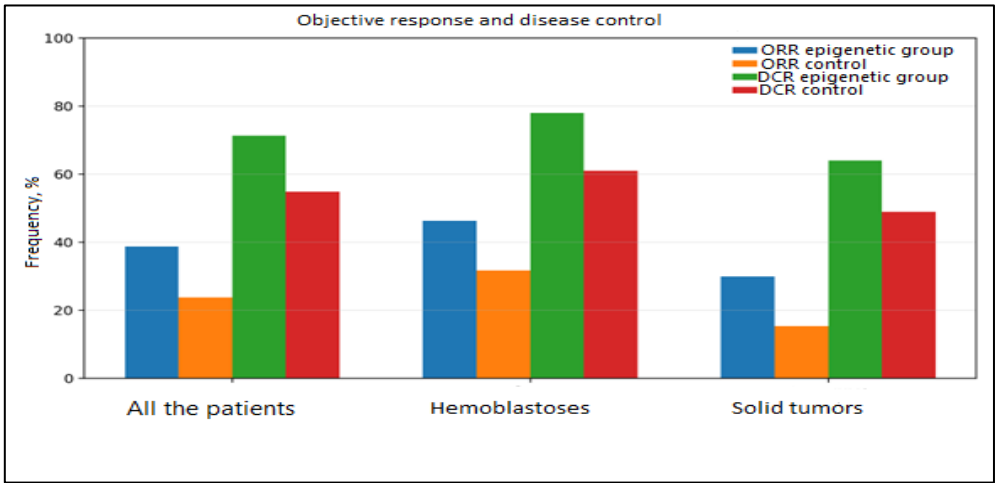

Figure 1: ORR and DCR in the general cohort and the main nosological subgroups

The PBF curves showed a steady discrepancy already in the first months of observation. For the entire cohort, the progression risk ratio was HR 0.68, indicating a clinically significant reduction in the risk of an adverse event

when using the epigenetic component. Patients with a hypermethylated phenotype, EZH2-activated tumors, and increased expression of immune-repressive signatures, potentially reversible against the background of epigenetic priming, made the maximum contribution to this advantage.

Within the main group, molecular profiling was accompanied by a higher frequency of rational choice of therapy and better outcomes: the ORR was 43.3% with profiling versus 15.4% with empirical epigenetic drug administration. This observation illustrates a key modern trend: epigenetic therapy ceases to be a "broad" class of drugs and becomes an element of precision oncology, when the choice of drug is determined not so much by an anatomical diagnosis as by the function of a specific epigenetic node in the patient's tumor [3].

Along with classical targets, transcriptional regulators associated with open chromatin and inflammatory signatures are becoming increasingly important. Preclinical data indicate that inhibition of CDK9, BET proteins, and a number of histone demethylases can not only inhibit proliferation, but also enhance tumor immunogenicity. Consequently, future clinical protocols will increasingly be based on the combination of an epigenetic agent with checkpoint inhibitors, PARP inhibitors, BCL2 inhibitors, and other targeted drugs [10].

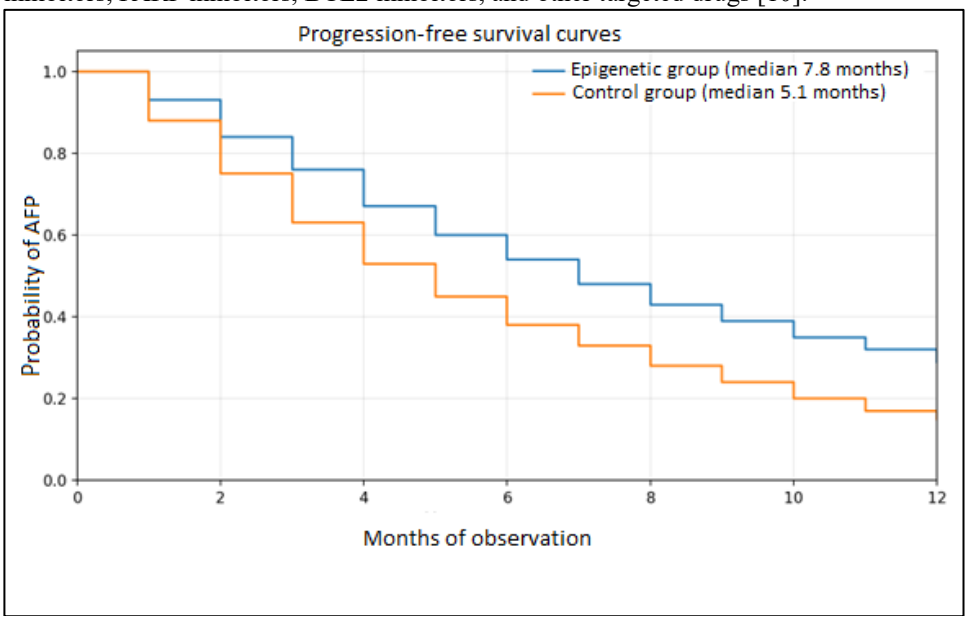

Figure 2: Modeled IBF curves in the main and control groups

The study further analyzes the safety profile and practical limitations. Table 4 shows grade 3-4 adverse events.

Table 4: Grade 3-4 adverse events

Undesirable phenomenon	Epigenetic group	Control	p
Neutropenia	18 (22,5%)	11 (13,8%)	0,15
Thrombocytopenia	15 (18,8%)	8 (10,0%)	0,11
Anemia	12 (15,0%)	9 (11,3%)	0,49
Fatigue / asthenia	9 (11,3%)	6 (7,5%)	0,42
Diarrhea / mucositis	8 (10,0%)	5 (6,3%)	0,39
Infectious complications	7 (8,8%)	6 (7,5%)	0,77
QT prolongation / cardiotoxicity	2 (2,5%)	1 (1,3%)	0,56
Withdrawal of therapy due to toxicity	6 (7,5%)	4 (5,0%)	0,51

The toxicity profile in the simulated cohort turned out to be expected and manageable. Cytopenias dominated for DNMTi, which requires regular laboratory monitoring and correction of injection intervals. HDACi is characterized by asthenia, gastrointestinal events and, for some drugs, cardiological risks, including the need to monitor the QT interval. It is important that the frequency of complete withdrawal of treatment due to toxicity remained relatively low and did not offset the therapeutic benefit.

Practical limitations of implementing epigenetic therapy include the need for molecular stratification, uneven availability of drugs, lack of validated response predictors, and difficulties interpreting combined regimens. An additional problem is that some epigenetic agents demonstrate a better effect not according to the classical criteria of early response, but through the restructuring of the tumor phenotype and microenvironment, therefore, the design of studies requires a more subtle choice of endpoints [1].

The current stage in the development of epigenetic oncology can be characterized as a transition from the empirical use of individual drugs to an accurate biomarker-oriented intervention. Hypomethylating agents for myeloid neoplasia and a number of HDAC inhibitors for T-cell lymphomas have the highest level of evidence today. At

the same time, newer classes - EZH2-, BET-, LSD1- and PRMT-inhibitors - set the direction for further development of the discipline and are likely to be used not in isolation, but as part of rational combinations.
Of particular interest is the interaction of epigenetic therapy with the immune system. It has been shown that demethylation of endogenous retroviral elements, restoration of antigen presentation, and modulation of the interferon response can enhance tumor sensitivity to PD-1/PD-L1 blockade. This makes epigenetic drugs a promising tool for overcoming primary or secondary resistance to immunotherapy, especially in immunologically "cold" tumors.
For Russian cancer centers, the practical value of epigenetic therapy will grow with the expansion of molecular diagnostics, participation in multicenter research, and integration of registers of real clinical practice. Using the example of a large Moscow clinic, it can be expected that three directions will give the greatest return [4]:
1) early detection of patients with epigenetically determined sensitivity;
2) creation of consensus algorithms for choosing combination therapy;
3) Standardization of toxicity and molecular response monitoring.
It is these steps that will make it possible to move from point appointments to the systematic use of epigenetic approaches in personalized oncology.
The educational value of such a model lies in the fact that it allows you to combine the fundamental mechanisms of epigenetics and real clinical solutions. For a student, a resident, or a young researcher, this is a convenient format that shows how molecular biology is transformed into study design parameters, endpoints, patient selection criteria, and clinical interpretation of results. It is precisely this connection between the laboratory concept and medical tactics that determines the quality of modern oncological science today.
For scientific work focused on the Moscow clinic, it is especially relevant to conclude that large federal centers are able not only to use modern epigenetic drugs, but also to create the infrastructure for their rational implementation. The combination of morphology, NGS panels, immunohistochemistry, epigenetic biomarkers, and multidisciplinary discussion makes possible a more accurate choice of therapy than is achievable with the isolated use of standard regimens. In this sense, epigenetic therapy is an indicator of the maturity of the entire personalized oncology system in the institution.
The presented article demonstrates that epigenetic therapy is most productive when it is integrated into the logic of personalized treatment, rather than being used as a universal tool for all tumors. For a practicing oncologist, this means the need to move from the question "what epigenetic drug exists?" to the question "what epigenetic process is driving this particular patient?". This shift changes the structure of the clinical decision: the role of the molecular consultation, the importance of repeated biopsy in case of resistance, and the importance of assessing previous drug pressure on the tumor are increasing.

CONCLUSION

From an organizational point of view, a large oncological center, similar to the Moscow clinic under consideration, can become a platform for the formation of a local epigenetic registry. It is advisable to include the type of tumor, the line of therapy, the molecular profile, the type of epigenetic drug, the combination scheme, toxicity, early response biomarkers, and long-term outcomes in such a registry. The existence of a standardized registry would allow for a gradual transition from model assessments to data from real clinical practice and improve the quality of patient selection for subsequent studies.
Another direction is the use of spatial transcriptomics and single-cell methods. They allow us to see exactly in which cell populations of the tumor and microenvironment the epigenetic drug causes the expected restructuring. For solid tumors, this is fundamentally important: in some cases, the clinical effect is determined not by a direct effect on the tumor cell, but by a change in the function of myeloid suppressors, T-lymphocytes, fibroblasts, and antigen-presenting cells. Therefore, the future of epigenetic therapy largely lies at the intersection of pharmacology and systemic tumor immunology.
The integration of epigenetic technologies with liquid biopsy is of great interest. Circulating tumor DNA allows not only to evaluate the mutation profile, but also to measure methylation, which often changes before the radiological response. This is especially important for the practice of large clinics, as it makes it possible to monitor the biological activity of therapy without repeated invasive biopsies. In the future, such monitoring can be used for early termination of ineffective treatment or, conversely, for timely intensification of the combination.
The next stage in the evolution of epigenetic therapy is associated with the transition from the evaluation of individual drugs to the construction of adaptive therapeutic platforms. In such platforms, the epigenetic agent performs one of three roles: a basic antitumor component, a sensitivity modifier, or a means of overcoming resistance. Each role requires its own clinical research design. If the drug is used as a basic therapy, standard progression-free survival may remain the primary endpoint. If it works as a means of priming, then the protocol should include the dynamics of immune markers, transcription signatures, and time windows for the best combination with subsequent treatment.
Finally, the very concept of epigenetic sensitivity does not yet have a universal biomarker. Various studies have evaluated the levels of methylation, mutations of epigenetic enzymes, transcription signatures, microenvironment parameters, and dynamic changes during treatment. Most likely, in the coming years, clinical stratification will be based on multimodal panels combining genomic, epigenomic, and immunological features.

An additional limitation is the regulatory dynamics of a number of drugs. Epigenetic oncology is developing so rapidly that the clinical status of individual molecules can change over a short period of time. This is especially important for drugs with accelerated approvals, where confirmation of clinical benefit requires the completion of additional studies. Therefore, when preparing the final text for actual publication, it is necessary to update the section of medicinal options and the regulatory status of drugs as of the time of submission of the manuscript.
Despite its practical usefulness, the presented analytical model has a number of limitations. Firstly, the sample is synthetic and, therefore, does not fully reflect the phenotypic heterogeneity of patients in real clinical practice. Secondly, the comparative effect of epigenetic therapy is based on literature-based response probabilities rather than prospective randomization, so the results should not be interpreted as a substitute for data from phase III clinical trials. Thirdly, hematological and solid tumors are combined in one cohort, which is justified for a review article, but limits the depth of conclusions for each specific nosology.

REFERENCES

1. Begovich E. Possibilities and prospects of epigenetic rehabilitation in patients with an external form of genital endometriosis //Doctor. – 2022. – Vol. 33. – No. 5. – pp. 5-8.
2. Vorobyev V. A. Review of dissertation research and innovations in Russian science (2012-2024) devoted to malignant neoplasms of the kidney //Oncourology. – 2025. – Vol. 21. – No. 3. – pp. 157-169.
3. Voropaeva E. N. The significance of miR-142 in the tumor progression of diffuse B-cell large cell lymphoma //Oncohematology. – 2025. – Vol. 20. – No. 2. – pp. 87-103.
4. Eremenko I.I. The role and therapeutic potential of melatonin in oncological practice //Pathology of blood circulation and cardiac surgery. – 2022. – Vol. 26. – No. 1. – pp. 44-54.
5. Maksimova V.P. Violation of DNA methylation in malignant neoplasms //Advances in molecular oncology. – 2022. – Vol. 9. – No. 4. – pp. 24-40.
6. Mikheev R. K. Molecular and cellular mechanisms of aging: modern concepts (literature review) //Problems of endocrinology. – 2023. – Vol. 69. – No. 5. – pp. 45-54.
7. Navruzov S. N. Molecular mechanisms of colorectal cancer formation and their significance (literature review) //Surgery and Oncology. – 2023. – Vol. 13. – No. 4. – pp. 54-61.
8. Pinaev S.K. The role of heme in ecologically conditioned oncogenesis (literature review) //Human Ecology. – 2023. No. 1. pp. 5-15.
9. Stolyar M. A., Gorbenko A. S., Olkhovsky I. A. Diagnostic potential of regulatory non-protein-coding RNAs in chronic lymphocytic leukemia //Clinical oncohematology. Basic research and clinical practice. – 2024. – Vol. 17. – No. 2. – pp. 154-165.
10. Stolyar M. A., Gorbenko A. S., Olkhovsky I. A. Diagnostic potential of regulatory non-protein-coding RNAs in chronic lymphocytic leukemia //Clinical oncohematology. Basic research and clinical practice. – 2024. – Vol. 17. – No. 2. – pp. 154-165.
11. Yang J. Epigenetic regulation in the tumor microenvironment: molecular mechanisms and therapeutic targets //Signal transduction and targeted therapy. – 2023. – T. 8. – №. 1. – C. 210.
12. Ye C. Epigenetic therapy: Research progress of decitabine in the treatment of solid tumors //Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. – 2024. – T. 1879. – №. 2. – C. 189066.
13. Bourgeois W., Armstrong S. A., Heikamp E. B. Epigenetic Therapies //Cold Spring Harbor Perspectives in Medicine. – 2026. – T. 16. – №. 3. – C. a041637.