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Current progress in the study of acute myeloid leukemia

Abstract. In recent years the rate of malignant diseases has been growing rapidly around the world. The Republic of Kazakhstan, according to international statistics, refers to the countries with moderately high cancer incidence and mortality. Every year approximately thirty thousand Kazakhstani people are diagnosed with cancer. In 2018, 35,753 patients were registered in the country, of which 44.3% were men and 55.7% were women. Cancer mortality over the same period amounts to about 15,000 lives. The cancer incidence rate increased by 8% from 181.2 (in 1999) to 195.7 per 100,000 population in 2019 [1]. Blood cancers are relatively rare diseases but, nevertheless, in Kazakhstan about 7,000 patients with hematopoietic malignancies are currently registered. Therefore, our knowledge of recent advances in hemato-oncology is highly relevant for successful therapy of these malignancies. In this review we provide information on the subtypes, symptoms, diagnosis and treatment of acute myeloid leukemia (AML) – one of the most aggressive blood cancer.

Key words: acute myeloid leukemia, cancer, anemia, FLT3, flavopyridol, HDAC inhibitor, PAP, targeted therapy.

Cancer is a major health problem facing the entire world, and Kazakhstan is not the exception. Currently, according to Kazakhstan statistics, blood cancer is one of the ten most common oncological diseases. There is a tendency for a slight increase in the incidence over the past ten years. The situation in the rest of the world is similar. One possible explanation is the improvement in diagnostic methods. Lymphomas and leukemias are most common in the industrialized countries, such as the USA, Switzerland and other European countries. Low rates of these cancers are recorded in Asian countries. In Kazakhstan, metrics are lower than in European countries. Chronic lymphocytic leukemia is more common in the Caucasian race. But it is also found among Asians and Kazakhs. There is also a tendency towards a "rejuvenation" of the blood cancer which has faced an epidemiological crisis due to an increase in the country's population. Totally, 6 741 new cases of leukemia were registered in Kazakhstan during the 2003-2012 period. The mean age of patients with leukemia was 48.5. The age-standardized incidence rates for leukemia among men and women were 5.3 and 3.6, respectively ($p<0.001$) [2].

It is known that cancer of the blood or hemoblastosis is a serious disease that can arise in men, women and even children, during the course of which blood-forming organs are affected. Malignant neoplasms which occur in the bone marrow are called leukemias. In addition to leukemias hemoblastoses include diseases such as hematosarcomas and lymphomas, which are extra-bone marrow growths of blast cells. Over time, tumor cells in hematosarcomas and lymphomas can spread to the bone marrow [3]. The causes of hemoblastoses are chemical carcinogenic agents, radiation or inherited genetic and epigenetic aberrations. Various carcinogens, acting on the hematopoietic cell genome, cause the transformation of its normal genetic program into a program for the formation of malignant neoplasms [4].

Acute myeloid leukemia (AML) is an aggressive clonal oncohematological disease associated with damage to the genetic material in hematopoietic stem and/or progenitor cells. Genetic and epigenetic transformation results in an appearance of immature myeloid blast cells which lack the ability to differentiate and are characterized by rapid uncontrolled proliferation. This leads to suppression of normal hematopoiesis due to replacement of normal bone marrow blast cells with leukemic blasts. There are several subtypes of AML, including monoblastic leukemia, acute promyelocytic leukemia, monocytic leukemia, megakaryocytic leukemia and erythroblastic leukemia and there are also mixed acute leukemia forms (Figure 1).

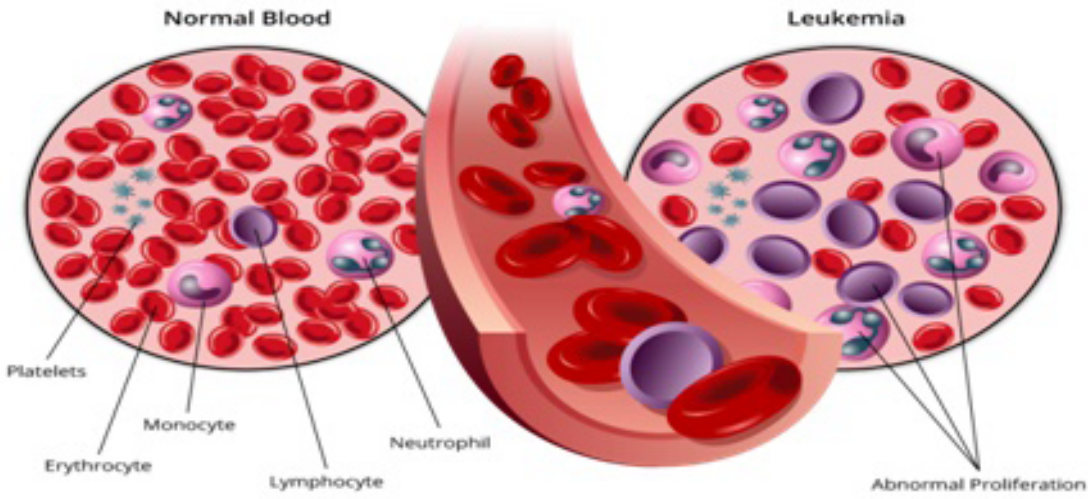

Figure 1 – General scheme for blood changes during leukemia (https://westcancercenter.org)

Laboratory tests, including cytomorphological, immunological and genetic analyses are employed to diagnose specific AML subtypes.

The fact that the pathogenesis of acute leukemia is associated with genetic breakdowns is often confirmed by the discovery of various chromosomal aberrations, translocations, deletions, inversions, etc. In most cases, the specific cause of AML remains unknown. However, there are several predisposing factors that significantly increase the risk of developing this disease. The clearly proven relationship between chemotherapy and/or radiotherapy for other tumors and an increased risk of acute leukemia, made many research groups study other possible leukemogenic factors, such as low doses of radiation, various chemicals, smoking, and electromagnetic waves. For instance, clear dose dependence has been proven between smoking and the risk of developing acute leukemia, that is especially evident for people over 60 years of age. A number of reports suggest that about 20% of AML are due to smoking. Prolonged exposure of the human body to benzene has a leukemogenic effect, but at low concentrations of this substance, which people most often encounter in the workplace, the relationship with an increased risk of AML is not proven.

In studying the effects of continual low-dose radiation, evidence has not yet been obtained in favor of an increase in the incidence of acute leukemia. For the first time, the relationship between previous chemotherapy or radiation treatment of other tumor diseases and an increased risk of AML was observed in patients cured of lymphogranulomatosis. It has been shown that not so much the cumulative dose as the dose intensity of the exposure is associated with an increase in the incidence of AML. The risk of developing secondary AML is highest between 2 and 9 years after completion of previous chemotherapy. In 85% of cases, secondary leukemia occurs within up to 10 years from the end of treatment [5; 6]. Children and adolescents with a specific congenital or acquired immunodeficiency, certain chromosomal abnormalities, diseases Down syndrome, Fanconi anemia, have a high predisposition to get sick with develop one of the forms of myeloid leukemia.

In the course of leukemogenesis, when diseased cells displace healthy ones, anemia, various infectious complications and frequent bleeding are observed. These are the first symptoms that can speak of acute leukemia. Other symptoms, such as fatigue, general weakness, sickness, fever, abdominal pain, loss of appetite are very often observed. Enlarged lymph nodes are noted. If leukemia cells enter the central nervous system, then cranial nerves can be paralyzed and breathing becomes difficult [7; 8]. AML, like all other types of leukemia, is a systemic malignant disease, that is, from the bone marrow it rapidly spreads into the bloodstream, lymphoid tissues and other organs. If acute leukemia is not treated, then death occurs in a few weeks or months.

Among all forms of cancer in children and adolescents, AML accounts for about 4.2% cases. According to German medical statistics, about 80 children and adolescents aged 0 to 14 years with a diagnosis of AML are registered annually in the Children's Cancer Register (Mainz), and the total number of patients with leukemia under the age of 18 is approximately 100 people a year [9; 10]. However, this

disease primarily targets older individuals and the median age of AML patients in general is about 68.

Carcinogenesis can be induced by chemical agents that are part of the food, and compounds used in various fields of industry. More than 1,500 organic and inorganic chemical compounds are potentially carcinogenic. Physical carcinogens include radioactive substances containing ^{32}P, ^{131}I, ^{90}Sr and other isotopes, x-rays and ultraviolet radiation. DNA – the main target of carcinogenic agents – is exposed either to their direct action or through mediators of carcinogenesis, including free radicals of oxygen, lipids and other organic and inorganic substances. Oncogenic viruses can also cause the development of blood cancers. For instance, the Epstein – Barr virus leads to the development of Burkitt's lymphoma, the human T-cell leukemia virus type I leads to T-lymphocytic leukemia. Retroviruses, adenoviruses and adeno-associated viruses can integrate into the human blood-forming cell genome and cause their oncogenic transformation. By the type of viral nucleic acid, oncogenic viruses are divided into DNA- and RNA-containing. Some oncoviral genes can play the role of promoters of cellular proto-oncogenes [11].

The mainstream treatment of AML is intensive chemotherapy with drugs that block cell growth or induce cytotoxicity. One such drug cannot kill all tumor cells, thus modern therapeutic approaches employ combinations of different cytostatics, cytotoxic agents and/or targeted drugs that act on cancer cells in different ways. Using these approaches it becomes possible, in some cases, to completely kill leukemia cells throughout the body so that the bone marrow can again earn as a hematopoietic organ. The initial stage of AML management is induction chemotherapy when a particularly intensive treatment is carried out in order to kill a maximum of leukemia cells within a short time. The next stage is consolidation therapy, which aims at destroying those leukemic cells that could survive the induction stage. The standard drug combination used in induction chemotherapy of AML is cytarabine and one of anthracyclines. Yet, the clinical outcomes remain to be poor, especially for those patients who are older or carry other higher-risk diseases. In recent years, extensive research has led to the development and characterization of novel agents which target AML by diverse mechanisms [12]. Among these are targeted therapeutics such as kinase inhibitors and oligonucleotide constructs. These aim to suppress the production or activity of oncogenic proteins, such as FLT3 and BCL2, and thus disrupt related signaling cascades essential for leukemogenesis and blast cell proliferation. Other agents, e.g., flavopiridol target myeloid blasts by suppression of cyclin-dependent kinases and interference with nucleotide synthesis. Another class of novel therapeutics includes histone deacetylase inhibitors, which cause growth arrest and apoptosis through histone acetylation and resultant conformational changes [13].

Bone marrow/hematopoietic stem cell transplantation is a method of choice in various hematological, oncological and autoimmune diseases in which, after intensive immunosuppressive therapy with high doses of cytostatic drugs, immunosuppressants, the patient is injected with pre-harvested bone marrow or peripheral blood hematopoietic stem/progenitor cells. The patients most in need of this method of treatment are those suffering from highly aggressive lymphomas, which make up 70% of all forms of lymphomas and leukemias. As a rule, these are young, potentially fit people. According to preliminary estimates, the need for about 1000 hematopoietic stem cell transplants arises annually in the Republic of Kazakhstan [14].

This review presents an overview of preclinical and clinical studies of selected promising small molecule compounds that are currently tested for a potential antileukemic activity. Differential therapy is an alternative or complementary treatment for AML, which aims at causing maturation of poorly differentiated leukemic blasts. The physiological form of vitamin D, 1,25-dihydroxyvitamin D_3 (1,25D3) is a steroid-like hormone with pleiotropic properties. These include important contributions to the control of cell proliferation, survival and differentiation, as well as the regulation of immune responses. This hormone also has a role in normal hematopoiesis, enhancing monocyte-macrophage differentiation. It also has antiproliferative and prodifferentiation effects against various myeloid leukemia cell lines and AML blasts *ex vivo*. Nevertheless, hematopoiesis in mice with vitamin D receptor (VDR) deletion is essentially normal, indicating that in mammals the vitamin D pathway appears to have a nonessential but perhaps a contributory role in blood formation [15].

Clinical trials with 1,25D3 have been performed for the treatment of preleukemia/myelodysplastic syndrome and AML, but the 1,25D3 doses effective *in vitro* caused severe hypercalcemia *in vivo*. Numerous vitamin D analogs with reduced calcemic activity have been synthesized which exhibit increased ability to induce cell differentiation and to inhibit proliferation of leukemic cells in preclinical model systems. Although such analogs have also been tested in trials, either alone or combined with other

agents, the therapeutic outcomes were inconclusive and hypercalcemia remained the major issue. The reasons for the unimpressive results of most clinical studies of the therapeutic effects of vitamin D derivatives (VDDs) in leukemia and related diseases may include the lack of a precise rationale for the conduct of these studies. Further, clinical trials to date have generally used extremely heterogeneous patient populations and, in many cases, small numbers of patients, generally without controls [16]. The available or new VDDs combined with other differentiating or antiproliferative agents, each working through different pathways, are expected to demonstrate synergistic activity and offer improved therapy for AML [15].

There is evidence that vitamin D_2 is less toxic than vitamin D_3 in animals. Recently, the research group led by M. Danilenko has determined the differentiation effects of several novel analogs of 1α,25-dihydroxyvitamin D_2 (1,25D2), including PRI-1916 and PRI-1917, in which the extended side chains of their previously reported precursors (PRI-1906 and PRI-1907, respectively) underwent further 24*Z* (24-*cis*) modification [17]. Using four human AML cell lines representing different stages of myeloid maturation (KG-1a, HL60, U937, and MOLM-13), it was found that the potency of PRI-1916 was slightly higher or equal to that of PRI-1906 while PRI-1917 was significantly less potent than PRI-1907. It was also demonstrated that 1,25D2 was a less effective differentiation agent than 1,25D3 in these cell lines. Irrespective of their differentiation potency, all the vitamin D_2 derivatives tested were less potent than 1,25D3 in transactivating the DR3-type vitamin D response elements (VDREs).

The data presented in Table 1 and Figure 3 demonstrate that PRI-1907 has much higher differentiation efficiency than PRI-1906 in all used AML cell lines. However, the effect of the new 24*Z* modification on the activities of PRI-1906 and PRI-1907 was different. Thus, the activity of PRI-1916 was slightly higher or equal to the effectiveness of PRI-1906, which contains naturally occurring alkyl branches at C-25. On the other hand, it was found that the activity of PRI-1917 in four cell lines was consistently lower compared to PRI-1907 containing homologated chains on C-25 (Table 1).

Table 1 – Comparative differentiation-inducing potencies of vitamin D derivatives in acute myeloidleukemia (AML) cells

Compounds	HL60	U937	MOLM-13	KG-1a
1.25D3	4.58 ± 0.34	1.97 ± 0.19	1.45 ± 0.09	8.65 ± 0.42
1.25D2	8.71 ± 0.62 *	4.31 ± 0.66 *	1.86 ± 0.15	32.29 ± 4.52 **
PRI-1906	4.88 ± 0.02	2.51 ± 0.28	1.67 ± 0.10	4.72 ± 0.97
PRI-1916	3.45 ± 0.07 *	2.87 ± 0.43	1.19 ± 0.08	5.85 ± 1.24
PRI-1907	0.42 ± 0.06	0.56 ± 0.08	0.19 ± 0.02	1.27 ± 0.04
PRI-1917	3.90 ± 0.15 ##	2.92 ± 0.51 ##	0.57 ± 0.04 #	4.87 ± 0.42 #

Cells were incubated with the indicated agents or vehicle ≤ 0.2% ethanol) for 96 h. The expression of CD14 and CD11b was determined by flow cytometry. EC_{50} values (nM) were calculated by non-linear regression analysis of the dose-response curves for the $CD14^+CD11b^+$ double-positive cell population. The percentage of the double-positive CD14+CD11b+ cell population is presented on Figure 2.

Plant polyphenols have been shown to potentiate the differentiation of AML cells induced by low, non-toxic concentrations of 1,25D3 and other VDDs. The enhanced antileukemic effects of these combinations may constitute the basis for the development of novel approaches for differentiation therapy of AML. Studies conducted by M. Danilenko's laboratory have shown that carnosic acid (CA), curcumin and silibinin (SIL) synergistically enhanced 1,25D3-induced differentiation of myeloblastic HL60 cells. However, in promonocytic U937 cells, only CA caused potentiation while SIL attenuated 1,25D effect [18]. The enhanced effect of 1,25D+CA was accompanied by increases in both the VDR and retinoid X receptor alpha (RXRα) protein levels and transactivation in both cell lines. Similar increases were observed in HL60 cells treated with 1,25D + SIL. In U937 cells, however, SIL inhibited 1,25D-induced VDRE transactivation concomitant with downregulation of RXRα at both transcriptional and posttranscriptional levels.

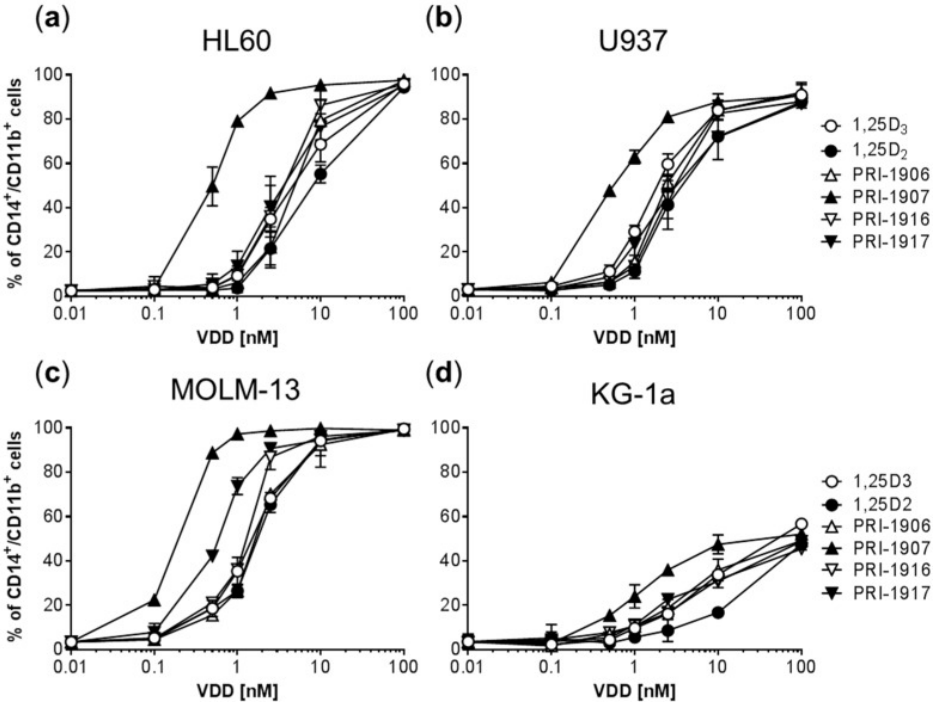

Figure 2 – Comparison of the differentiation-inducing effects of different vitamin D derivatives on AML cells (a–d). The data are the means ± SD of at least four independent experiments; *, p< 0.05 vs. 1,25D3; **, p< 0.01 vs. 1,25D3; #, p< 0.05 vs. PRI-1907; ##, p< 0.01 vs. PRI-1907 [17]

How the above phytochemicals modulate VDDs effects in different subtypes of AML cells is not yet fully understood. However, it has been demonstrated that the transcription factor Nrf2 and the Nrf2//antioxidant response element (Nrf2/ARE) signaling pathway mediate the differentiation-enhancing effects of plant polyphenols [19]. Particularly the inhibitory effects of SIL on 1,25D3-induced differentiation of U937 cells correlated with the inability of SIL, with or without 1,25D3, to activate the Nrf2/ARE pathway in these cells. These results suggest that opposite effects of SIL on 1,25D3-induced differentiation of HL60 and U937 cells may be determined by cell-type-specific signaling and transcriptional responses to this polyphenol resulting in differential modulation of RXRα expression [18]. Interestingly, similar to 1.25D3, both 1.25D2 and its analogs could strongly cooperate with CA in inducing cell differentiation and inhibition of G1-S cell cycle transition [17]. Most recently, it has been demonstrated that activators of Nrf2 other than polyphenols, including clinically approved drug dimethyl fumarate, can also markedly potentiate the antileukemic effects of VDDs on AML cells both *in vitro* and *in vivo* [21].

Besides their differentiation-enhancing activity, VDD/CA combinations can also potentiate the cytotoxic effects of chemotherapeutics. Thus, it has been found that the combination of the clinically approved vitamin D_2 analog doxercalciferol and CA (D2/CA) significantly increases the extend of AML cell death caused by a low concentration of arabinosylcytosine (AraC) [21, 22]. Notably, although AraC-induced cytotoxicity was accompanied by the increased generation of intracellular reactive oxygen species (ROS), the enhancement of cell death by D2/CA was accompanied by a decrease in ROS levels and by activation of VDR-dependent signaling pathway leading to ASK1-mediated apoptosis.

Plant-derived phenolic compounds are capable of cooperating with one another against different types of malignant cells. Particularly, studies by M. Danilenko's laboratory have demonstrated that curcumin (CUR) or methyl 4-hydroxycinnamate (MHC) can uniquely synergize with CA at non-cytotoxic concentrations of each agent, producing massive apoptotic cell death in different AML cell lines [23, 24]. The CUR+CA combination also demonstrated a marked antileukemic effect in vivo [24]. Importantly, these combinations did not affect normal hematopoietic cells. Mechanistically, MHC+CA- and CUR+CA-induced apoptosis was mediated solely by the disruption of cellular Ca^{2+} homeostasis. Ac-

tivation of caspase cascade in combination-treated AML cells resulted from sustained elevation of cytosolic Ca^{2+} (Ca^{2+}_{cyt}) and was not preceded by endoplasmic reticulum stress or mitochondrial damage. The CUR+CA-induced Ca^{2+}_{cyt} rise did not involve excessive influx of extracellular Ca^{2+} but, rather, occurred due to massive Ca^{2+} release from intracellular stores concomitant with inhibition of Ca^{2+}_{cyt} extrusion through the plasma membrane. Collectively, these results provide the mechanistic and translational basis for further characterization of MHC+CA and CUR+CA combinations as ~~a~~ prototypes of novel Ca^{2+}-targeted pharmacological tools for the treatment of AML [25, 26].

The socio-economic problem of blood cancer is currently extremely relevant, taking into account not only the high mortality rate, but also the disability of patients, the huge material costs during treatment. Therapy of AML still remains a challenge. As survival of patients has not changed significantly over the years, ~~and~~ new strategies are urgently needed. Some anticancer agents, such as flavopiridol, have shown promising results in commercially developed AML clinical trials. Others, such as those that target individual signaling proteins, are already approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of different AML subtypes. In addition, we describes novel promising approaches based on the use of combinations of natural agents, which deserve further detailed discussion beyond the scope of our review. Future therapeutic modalities in AML include immunomodulation with vaccines as well as targeting leukemic microenvironment, leukemia stem cells, and oncogenic fusion proteins or transcription factors involved in leukemogenesis. Overall, it is hoped that continued progress in expanding new approaches will soon provide useful additions to AML therapy and will significantly improve its currently poor prognosis.

References

1. Howlader N., Noone A.M., Krapcho M., Miller D., Brest A., Yu M., Ruhl J., Tatalovich Z., Mariotto A., Lewis D.R., Chen H.S., Feuer E.J., Cronin K.A. (eds). SEER Cancer Statistics Review, National Cancer Institute, 2019.

2. Igissinov N., Kulmirzayeva D., Moore M.A., Igissinov S., Baidosova G., Akpolatova G., Bukeyeva Z., Omralina Y. (2014) Epidemiological assessment of leukemia in Kazakhstan, 2003- 2012. *Asian Pac J Cancer Prev.*, vol. 15, no. 16, pp. 6969-6972.

3. Shinkevich D.S., Mikhailova E.A., Parovichnikova E.N., Troitskaya V.V. (2015) Clinical and morphological manifestations of hemoblastosis in the maxillofacial region. Tactics of surgical dental care for patients with hemoblastoses. *Rus dent*., vol. 8, no. 2, pp. 19-28.

4. Kumar V., Abbas A.K., Aster J.C. (2015) Robbins and Cotran pathologic basis of disease. Neoplastic proliferation of white cells, 9th ed., Philadelphia: Elsevier, pp. 586-622.

5. Savchenko V.G. (2012) Program treatment of diseases of the blood system. Moscow: Practice, pp. 155-245.

6. Savchenko V.G., Parovichnikova E.N. (2001) Acute leukemia. In: Clinical Oncohematology, Moscow: Medicine, pp. 156-207.

7. Swerdlow S.H., Campo E., Pileri S.A., et al. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, vol. 127, no. 20, pp. 2375-2390.

8. Arber D.A., Orazi A., Hasserjian R., et al. (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*, vol. 127, no. 20, pp. 2391-2405.

9. Campana D., Pui C.H. (2014) Childhood leukemia. In: Niederhuber JE, Armitage J.O., Doroshow J.H., Kastan M.B., Tepper J.E., eds. Abeloff's Clinical Oncology. 5th ed., Philadelphia, PA: Elsevier Saunders, 96.

10. Dahl G.V., Weinstein H.J. Acute myeloid leukemia in children (2005) In: Hoffman R., Benz E.J., Shattil S.J., Furie B., Cohen H.J., Silberstein L.E., McGlave P., eds. Hematology: Basic principles and practice. 4th ed., Philadelphia, Pa. Elsevier, pp. 1121-1133.

11. Litvitsky P.F., Zhevak T.N. (2016) Hemoblastoses. Leukemia of lymphoid origin. Questions of modern pediatrics, vol. 15, no. 5, pp. 457-470.

12. Bohl S.R., Bullinger L., Rücker F.G. (2019) New targeted agents in acute myeloid leukemia: new hope on the rise, *Int J Mol Sci*., vol. 20, p. 1983.

13. Fathi A.T., Grant S., and Karp J.E. (2010) Exploiting cellular path-ways to develop new treatment strategies for AML. *Cancer Treatment Reviews*, vol. 36, no. 2, pp. 142-150.

14. The Ministry of Health of the Republic of Kazakhstan, the Kazakhstan Research Institute of Oncology and Radiology. Comprehensive plan to combat cancer in the Republic of Kazakhstan for 2018-2022. 42 p.

15. Studzinski G.P., Gocek E., Coffman F., Danilenko M. (2018) Effects of vitamin D deriva-

tives on differentiation, cell cycle, and apoptosis in hematological malignancies. 4th ed., vol. 2: Health, Disease and Therapeutics, pp. 761-799.

16. Studzinski G.P., Harrison J., Wang X., Sarkar S., Kalia V., Danilenko M. (2015) Vitamin D control of hematopoietic cell differentiation and leukemia. *J Cel Biochem*., vol. 116, no. 8, pp. 1500-1512.

17. Nachliely M., Sharony E., Rao Bolla N., Kutner A., Danilenko M. (2016) Prodifferentiation activity of novel vitamin D_2 analogs PRI-1916 and PRI-1917 and their combinations with a plant polyphenol in acute myeloid leukemia cells. *Int J of Mol Sci*., vol. 17, no. 7, p. 1068.

18. Danilenko M., Wang Q., Wang X., Levy J., Sharoni Y. and Studzinski G.P. (2003) Carnosic acid potentiates the antioxidant and prodifferentiation effects of 1α,25-dihydroxyvitamin D_3 in leukemia cells, but does not promote elevation of basal levels of intracellular calcium. *Cancer Res.*, vol. 63, pp. 1325-1332.

19. Bobilev I., Novik V., Levi I., Shpilberg O., Levy J., Sharoni Y., Studzinski G.P., Danilenko M. (2011) The Nrf2 transcription factor is a positive regulator of myeloid differentiation of acute myeloid leukemia cells. *Cancer Biol Ther.*, vol. 11, pp. 317-329.

20. Nachliely M., Trachtenberg A., Khalfin B., Nalbandyan K., Cohen-Lahav M., Yasuda K., Sakaki T., Kutner A., Danilenko M. (2018) Dimethyl fumarate and vitamin D derivatives cooperatively enhance VDR and Nrf2 signaling in differentiating AML cells in vitro and inhibit leukemia progression in a xenograft mouse model. *J Steroid Biochem Mol Biol.*, vol. 188, pp. 8-16.

21. Wang X., Dawod A., Nachliely M., Harrison JS., Danilenko M., Studzinski G.P. (2019) Differentiation agents increase the potential AraC therapy of AML by reactivating cell death pathways without enhancing ROS generation. *J Cell Physiol.*, vol. 235, no. 1, pp. 573-586.

22. Studzinski G.P., Harrison J.S., Wang X., Sarkar S., Kalia V., Danilenko M. (2015) Vitamin D control of hematopoietic cell differentiation and leukemia. *J Cell Biochem*., vol. 116, no. 8, pp. 1500-1512.

23. Trachtenberg A., Muduli S., Sidoryk K., Cybulski M., Danilenko M. (2019) Synergistic cytotoxicity of methyl 4-hydroxycinnamate and carnosic acid to acute myeloid leukemia cells via calcium-dependent apoptosis induction. *Front Pharmacol*., vol. 10, no. 507, pp. 1-7.

24. Pesakhov S., Nachliely M., Barvish Z., Aqaqe N., Schwartzman B., Voronov E., Sharoni Y., Studzinski G.P., Fishman D., Danilenko M. (2016) Cancer-selective cytotoxic Ca^{2+} overload in acute myeloid leukemia cells and attenuation of disease progression in mice by synergistically acting polyphenols curcumin and carnosic acid. *Oncotarget*, vol. 7, no. 22, pp. 1-7.