ISSN 2518-1483 (Online),
ISSN 2224-5227 (Print)

2019 • 3

**ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ**

БАЯНДАМАЛАРЫ

ДОКЛАДЫ

**НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН**

REPORTS

**OF THE NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN**

PUBLISHED SINCE 1944

ALMATY, NAS RK

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ
БАЯНДАМАЛАРЫ **2019 • 3**

«Қазақстан Республикасы Ұлттық ғылым академиясының баяндамалары»
ISSN 2518-1483 (Online),
ISSN 2224-5227 (Print)

Меншіктенуші: «Қазақстан Республикасының Ұлттық ғылым академиясы» Республикалық қоғамдық бірлестігі (Алматы қ.)
Қазақстан республикасының Мәдениет пен ақпарат министрлігінің Ақпарат және мұрағат комитетінде 01.06.2006 ж. берілген **№5540-Ж** мерзімдік басылым тіркеуіне қойылу туралы куәлік

Мерзімділігі: жылына 6 рет.
Тиражы: 500 дана.

Редакцияның мекенжайы: 050010, Алматы қ., Шевченко көш., 28, 219 бөл., 220, тел.: 272-13-19, 272-13-18,
http://reports-science.kz/index.php/en/archive

Типографияның мекенжайы: «Аруна» ЖК, Алматы қ., Муратбаева көш., 75.

ДОКЛАДЫ **2019 • 3**
НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН

Доклады Национальной академии наук Республики Казахстан»
ISSN 2518-1483 (Online),
ISSN 2224-5227 (Print)

Собственник: Республиканское общественное объединение «Национальная академия наук Республики Казахстан» (г. Алматы)
Свидетельство о постановке на учет периодического печатного издания в Комитете информации и архивов Министерства культуры и информации Республики Казахстан **№5540-Ж**, выданное 01.06.2006 г.

Периодичность: 6 раз в год.
Тираж: 500 экземпляров

Адрес редакции: 050010, г.Алматы, ул.Шевченко, 28, ком.218-220, тел. 272-13-19, 272-13-18
http://reports-science.kz/index.php/en/archive

Адрес типографии: ИП «Аруна», г.Алматы, ул.Муратбаева, 75

REPORTS **2019 • 3**
OF NATIONAL ACADEMY OF SCIENCES OF THE
REPUBLIC OF KAZAKHSTAN

Reports of the National Academy of Sciences of the Republic of Kazakhstan.
ISSN 2224-5227
ISSN 2518-1483 (Online),
ISSN 2224-5227 (Print)

Owner: RPA "National Academy of Sciences of the Republic of Kazakhstan" (Almaty)
The certificate of registration of a periodic printed publication in the Committee of Information and Archives of the Ministry of Culture and Information of the Republic of Kazakhstan N 5540-Ж, issued 01.06.2006

Periodicity: 6 times a year
Circulation: 500 copies

Editorial address: 28, Shevchenko str., of.219-220, Almaty, 050010, tel. 272-13-19, 272-13-18,
http://reports-science.kz/index.php/en/archive

Address of printing house: ST "Aruna", 75, Muratbayev str, Almaty

REPORTS OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
ISSN 2224-5227 **https://doi.org/10.32014/2019.2518-1483.71**
Volume 3, Number 325 (2019), 51 – 55

UDK 615.1.4(175)

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THE PRECLINICAL EFFECT OF NATURAL DRUGS IN COMBINATION WITH CYTOSTATICS UPON THE GROWTH OF THE INITIAL AND DRUG-RESISTANT METASTASIS OF TUMORS

Abstract. The effect of various combinations of herbal preparations and anti-cancer compounds in rats with drug-resistant models of metastasis of Pliss's lymphosarcoma was studied. Obtained a pronounced antimetastatic effect alhidin combination with vincristine and alhidin with methotrexate in the experiments with the platform, resistant to rubomycin (lack of development of metastases in the inguinal lymph nodes, IL 174%). The combination of the effect of alidina to prospidine (ELE – extended life expectancy -308%) with an increase in immunological (cellular) indicators from them. Metastases did not develop in rats with metastasis of Pliss's lymphosarcoma resistant to lamattina from combinations of alhidin+cyclophosphamide, alhidin+sarcolysine and alhidin + prospidin + cyclophosphamide; ELE – extended life expectancy was 207%. Alhidin on mice with Lewis lung carcinoma as separately, and in combination with platidiam, cyclophosphamide and 5-fluorouracil caused a pronounced anti allergic effect: metastases did not develop 98% of the rats, ELE – extended life expectancy – 248%.

Key words: Sarcoma 45, Pliss lymphosarcoma, Lewis pulmonary carcinoma, melanoma B-16, drug resistance, herbal preparations.

As a result of years of research into the physiology and biochemistry of tumor cells, an important feature discovered for all tumors is the heterogeneity of the cell population. It is the heterogeneity of a tumor consisting of subpopulations of cells with different degrees of differentiation and growth rate that underlies progression, metastasis, and the emergence of drug resistance to it [1, 2]. The idea of heterogeneity of populations of tumor cells is crucial for the development of rational approaches to chemotherapy. If each tumor, even a highly differentiated one, contains a subpopulation of undifferentiated, actively dividing cells, then the cure of such a tumor is possible only with the combined using the anticancer drugs. Consequently, overcoming the emerging drug resistance of metastases can be expected only from combination therapy using two or more drugs with a different mechanism of action [1, 3, 4].

The emergence of drug resistance in metastases is often one of the main causes of the failure of modern specific treatment [5, 6, 9]. Taking into account these features, it was necessary to research the effect of the combination of new herbal preparations with cytostatics in animal experiments with the variants of drug-resistant metastases of Pliss lymphosarcoma that weaved under the skin of the tail from metastases developing in the inguinal lymph nodes [4, 7, 8].

The use of herbal preparations both individually and in combinations for metastases of Pliss lymphosarcoma of the original variant did not reveal any marked inhibition of tumor growth in the tail: the frequency of metastasis in rats decreased by 2.7 times, and the lengthening of the life extension of animals did not exceed 78%. On metastases of Pliss lymphosarcoma, a resistant variant to rubomycin, an inhibitory effect was noted against primary tumors in the tail of rats during treatment with alhidin and its

combination with SRS (80%, P <0.05, up to 128% of ELE – extended life expectancy). This combination caused a significant inhibition of tumors' growth and their resorption in 30% of rats with an increase in ELE to 174%, with no appearance of metastases in the inguinal lymph nodes. The combination of alhidine with methotrexate increased the ELE of animals with metastases of Pliss lymphosarcoma, a resistant variant to rubomycin, up to 142%, reducing the frequency of metastasis 7.6 times.

Histological studies of tissues of Pliss lymphosarcoma, a resistant variant for rubomycin, also found an active effect of this combination on cells.

In the control (Pliss lymphosarcoma), the tumor cells were round, often with soft pink rims of the cytoplasm, hyperchromic, oval and round, moderately polymorphic nuclei. The tumor cells were located tightly, forming different sized considerable layers separated by thin layers of connective tissue. When exposed to a combination of (Alhidin + Methotrexate), tumor cells were strongly scattered. Only a few retained the appearance of tumor cells, mostly small with pycnotic nuclei.

The same results were obtained in the treatment with sodium salt 1.2-3-keto-18-dehydroglycyrrhetic acid + Vincristine and sodium salt 1.2-3-keto-18-dehydroglycyrrhetic acid + cyclophosphamide: up to 106% and 123% ELE, respectively) and 7.6 times decrease metastasis frequency. However, a single use of drugs in these combinations did not increase ELE (80%) and reduced the frequency of metastasis only 3.8 times. Obviously, when applying this combination, therapeutic synergy from the combinants occurs.

A morphological study of metastases of Pliss lymphosarcoma resistant to rubomicin after exposure to the combination (sodium salt 1.2-3-keto-18-dehydroglycyrrhetic acid + cyclophosphamide) showed an altered histological picture in comparison with control: cells were located non-compact, without forming any structures, many different-sized foci. The nuclei of the cells are polychromic, and they were pyknotic and polygonal. The tumor had small foci of necrosis with moderate perifocal leukocyte reaction.

Natural preparations Alhidin compared with alnusidine, rubomisin and 5-fluorouracil on metastases of Pliss lymphosarcoma, both initial and resistant variants, caused the development of a primary tumor in the tail in only 30% of rats (inhibition of tumor growth to 63-75%), reducing 8.0-8.6 times metastasis in the inguinal limos nodes and an increase in ELE animals up to 95%. Pronounced inhibitory effect was obtained when exposed alhidin + rubomicin, alhidin + 5-fluorouracil + alhidin platidiam, alhidin + 5-fluorouracil and methotrexate + alnusidin where inhibition of tumor growth in the tail of rats with metastasis of Pliss lymphosarcoma, resistant to prospidin, amounted to 98% with the resorption of tumors (30%) in the absence of metastases in the inguinal lymph nodes and their immunodepressive reaction to the body with ELE to 308%. The combination of alhidin + cyclophosphamide moderately inhibited the growth of the primary tumor in the tail (63%, P <0.05) and significantly (8, 6 times) reduced the development of metastases in the inguinal lymph nodes.

Histological studies of metastases of Pliss lymphosarcoma, a resistant variant against prospidin, showed an inhibitory effect of these combinations. In the control, the tumor cells were settled scattered forming mainly around the numerous small vessels of the connective interlayers. In experimental variants of metastases, cells with polychromic nuclei were presented in the form of different-sized islands surrounded by foci of necrosis. On the periphery of necrosis, the tumor cells were polymorphic; their nuclei were in the state of pycnosis, rexis, lysis, often instead of nuclei - small clumps of chromatin.

Under the action of combinations of anticancer drugs (vincristine + cyclophosphamide) or (methotrexate + platidiam), the ELE of animals in this variant did not exceed 59 and 68%, respectively, although the incidence of metastasis decreased to 3.3 and 4.3% compared to control. Obviously, in these combinations, the summation of toxic effects takes place.

Different sensitivity of primary and metastatic tumors to chemotherapeutic effects was noted [2,4,10]. A comparative study of the properties of primary tumors and their metastases in the inguinal lymph nodes when exposed to combinations of herbal preparations with known antitumor compounds established the suppression of Pliss lymphosarcoma metastases (resistant variants) with incomplete inhibition of primary tumors in the tail. These results are coordinated with the data of some works on the higher susceptibility of metastases to the action of anticancer agents as compared with the primary tumor [2, 11, 12, 13, 14, 15].

In this case, there was revealed an interesting fact of appearance of the collateral sensitivity resistant to leucoephdin, Pliss lymphosarcoma, intertwined under the skin in the side during sarcolysin treatment (up to 95% growth inhibition with resorption of tumors in 30% of rats). In comparison with metastasis of Pliss lymphosarcoma resistant to leucoefdin, sarcolysin inhibited the growth of tumors in the tail (up to

80%, P <0.001) and reduced the frequency of metastases (up to 8%) of ELE to 126%. Obviously, with sarcolysin, collateral sensitivity is manifested in primary tumors, but the appearance of metastases in the inguinal lymph nodes is not completely inhibited. However, the combined effect of alhidin + sarcolysin, alhidin + cyclophosphamide at a therapeutic dose has a significant inhibitory effect (up to 98%, P <0.002) on primary tumors of rats with metastasis of Pliss lymphosarcoma resistant to leucoefdin, with resorption of tumors (60% of rats) and complete inhibition of the development of metastases (with ELE to 207%). Similar results were obtained by the combination of alhidin + prospidin + cyclophosphamide though using alhidin + prospidin was less effective.

The activity of herbal preparations and their combinations with cytostatics was also researched in mice with Lewis pulmonary carcinoma and melanoma B16 [6, 16, 17].

The use of alhidine in parallel with anticancer drugs (cyclophosphamide, platidiam) resulted in statistically reliable inhibitory growth of the main tumor site (up to 71%, P <0.05), 3.1 times reduced the number of metastases and 3.3 times the frequency of metastasis. The combinations of alhidin + platidiam and alhidin + cyclophosphamide led to the manifestation of antitumor (98%, P <0.001) with resorption of tumors in 60% of rats and antimetastatic effects (with ELE up to 260%). The use of alhidin + vinkristin + platidiam reduced the number of metastases by 3.9 times and the frequency of metastasis by 10% in the case of ELE - 139%.

Similar results were obtained when using sapponine, polysaccharides and sucrose monoesters in double and triple combinations with cytostatics. These vegetable compounds, having a moderate antitumor effect, are also able to intensify the selectivity of the action of anticancer drugs. A significant inhibitory effect was obtained from the use of (sucrose monoester + platidiam + alhidin) at half the maximum dose tolerated in experiments on mice with B-16 melanoma: the absence of metastases and the inhibition of growth of primary tumors (98%, P <0.001). The use of combinations of alhidin + platidiam, alnusidine + platidiam and monoester sucrose + platidiam reduced the frequency of metastasis in mice with B-16 melanoma only 3.6-4.5 times. The data obtained show that the herbal preparations (alhidin, alnusidine, sodium salt of 1.2-3-keto-18-dehydroglycyrrhetic acid, sapponine, polysaccharide, sucrose monoester) in the three models of recurrent tumors had a more pronounced antimetastatic effect as with isolated use, and in combination with anticancer drugs while reducing their toxicity. The mechanism of the antitumor action of herbal polyflavans (alhidin, ellagothannins, alnusidin) is likely to create a deficiency of kinins in the tumor capillaries, which disrupts the normal blood supply of the last, dilates the blood vessels and prevents the tumor cells from delay and settling in the capillary network [4, 10, 18, 19, 20].

The authors also proved that the introduction into the body of plant polyphenols, including flavonoids, which increase the antioxidant activity of animal tissues, increases the resistance of animals to the action of radiation with a significant increase in life expectancy [4, 10]. The data obtained give grounds to recommend the studied drugs for using in combined chemotherapy of malignant tumors and their metastases, especially for drug resistance to them. Herbal preparations have the ability to increase the selectivity of the action of cytotoxic drugs, enhancing their specific antitumor and, in particular, anti-metastatic activity against drug-resistant strains, protecting hemopoietic tissue from their toxic effect.

Thus, for the first time, we studied the effect of various variants of the combination of herbal preparations and antitumor compounds in rats with drug-resistant metastases of Pliss lymphosarcoma. A pronounced antimetastatic effect of the combination of alhidine with vincristin and alhidine with methotrexat was obtained in experiments with metastases of Pliss lymphosarcoma resistant to rubomycin: no development of metastases in the inguinal lymph nodes, ELE up to 174%. The complex effect of alhidine with rubomitsin, and alhidin with platidiam on the development of lymphosarcoma metastases resistant to prospidine: ELE to 308% with an increase in immunological (cellular) parameters in them. It was revealed that when using combinations: alhidine + cyclophosphamide, alhidine + sarkolysin and alhidin + prospidin + cyclophosphamide metastasis did not develop in rats with metastasis of Pliss lymphosarcoma resistant to leucoefdin, ELE animals at that was 207%. A pronounced antitumor effect (up to 98% inhibition of tumor growth) was shown under the action of combinations (sucrose monoester + 5-fluorouracil, sucrose monoester + adriamycin + saponin) in experiments on mice with Lewis pulmonary carcinoma and combinations (sucrose monoester + platidiam + alhidin) on animals with B-16 melanoma (ELE - up to 272%).

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БАСТАПҚЫ ЖӘНЕ ДӘРІГЕ ТҰРАҚТЫ МЕТАСТАЗДАРДЫҢ ӨСУІНЕ ЖАҢА ТАБИҒИ ПРЕПАРАТТАРДЫҢ ЦИТОСТАТИКТЕРМЕН БІРІКТІРГЕН КЕЗДЕГІ КЛИНИКАҒА ДЕЙІНГІ ӘСЕРІ

Аннотация. Инновациялық отандық өсімдік препараттарын және ісікке қарсы синтетикалық қосылыстарды Плисс лимфосаркомасының дәріге тұрақты метастаздарына біріктіріп қолдануды зерттедік. Алхидинді винкристинмен және алхидинді метотрексатпен бірге қолданғанда рубомицинге тұрақты Плисс лимфосаркомасының метастазына қарсы әсер көрсетті (шап лимфа түйіндерінде метастаздың болмауы, өмір сүру ұзақтығы 174%). Алхидинді рубомицинмен, алхидинді платидиаммен бірге қолданғанда проспидинге тұрақты Плисс лимфосаркомасының метастазын дамуын толығымен тежеді (өмір сүру ұзақтығы -308%), иммунологиялық көрсеткіштері жоғарылады. Лейкоэфдинге тұрақты Плисс лимфосаркомасының метастазын алхидин+циклофосфан, алхидин+сарколизин және алхидин+проспидин+циклофосфан қолданғанда егеуқұйрықтарда метастаз болған жоқ, өмір сүру ұзақтығы 207%. Алхидин өкпенің Льюис карциномасы бар тышқандарға жекелей және платидиаммен, циклофосфанмен және 5-фторурацилмен бірге қолданғанда айқын метастазға қарсы әсер көрсетті: 98% егеуқұйрықтарда метастаз болмады, өмір сүру ұзақтығы 248%.

Түйін сөздер: Саркома 45, Плисс лимфосаркомасы, дәріге тұрақты метастаздар, Льюис карциномасы, В-16 меланомасы, қатерлі ісікке қарсы синтетикалық препараттар.

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ДОКЛИНИЧЕСКОЕ ДЕЙСТВИЕ ИННОВАЦИОННЫХ ПРИРОДНЫХ ПРЕПАРАТОВ В КОМБИНАЦИИ С ЦИТОСТАТИКАМИ НА РОСТ ИСХОДНЫХ И ЛЕКАРСТВЕННО РЕЗИСТЕНТНЫХ МЕТАСТАЗОВ ОПУХОЛЕЙ

Аннотация. Изучено действие различных вариантов комбинаций инновационных отечественных растительных препаратов и противоопухолевых соединений на крысах с лекарственно резистентными моделями метастазов лимфосаркомы Плисса. Получен выраженный антиметастатический эффект комбинации алхидина с винкристином и алхидина с метотрексатом в опытах с метастазом лимфосаркомы Плисса, резистентной к рубомицину (отсутствие развития метастазов в паховых лимфоузлах, УПЖ 174%). Сочетание воздействия алхидина к проспидину (УПЖ-308%) приводит к повышению иммунологических показателей у них. Метастазы не развивались у крыс с метастазом лимфосаркомы Плисса, резистентной к лейкоэфдину от комбинаций: алхидин+циклофосфан, алхидин+ сарколизин и алхидин + проспидин + циклофосфан; УПЖ при этом составило 207%. Алхидин на мышах с карциномой легких Льюис как в отдельности, так и в сочетании с платидиамом, циклофосфаном и 5-фторурацилом вызывали выраженный противометастатический эффект: метастазы не развивались у 98% крыс, УПЖ – 248%.

Ключевые слова: саркома 45, лимфосаркома Плисса, карцинома легких Льюиса, меланома В-16, лекарственная резистентность, растительные препараты.

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Правила оформления статьи для публикации в журнале смотреть на сайте:

www:nauka-nanrk.kz

ISSN 2518-1483 (Online), ISSN 2224-5227 (Print)

http://reports-science.kz/index.php/en/archive

Редакторы *М. С. Ахметова, Т.А. Апендиев, Д.С. Аленов*
Верстка на компьютере *А.М. Кульгинбаевой*

Подписано в печать 6.06.2019.
Формат 60x881/8. Бумага офсетная. Печать – ризограф.
15,5 п.л. Тираж 500. Заказ 3.