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ANTITUMOR INHIBITION OF NATURAL DRUGS IN COMBINATION WITH CYTOSTATICS FOR DRUG-RESISTANT TUMORS

Abstract. Drug-resistant Pliss lymphosarcoma strains are resistant to both herbal and cytostatics, and sarcoma 45 is resistant only to synthetic drugs. Manifestation of cross, multiple resistance to both natural and well-known anticancer drugs in resistant strains of Pliss lymphosarcoma, sarcoma 45, lymphocytic leukemia L 1210 has place. Collateral sensitivity to known chemotherapy drugs was revealed in drug-resistant variants of Pliss lymphosarcoma and in new natural preparations in resistant strains of sarcoma 45, L 1210. Induced drug resistance of Pliss lymphosarcoma, sarcoma 45 and L 1210 is removed by new herbal compounds or their combinations with antitumor drugs, changing the dose and number of combinants.

The results of experimental studies for overcoming the emerged drug resistance with natural drugs in 1/2 MTD in a few (2 and 4) hours before the start of treatment with nitrosomethylurea, platidiam and adriamycin serve as a criterion for predicting clinical efficacy in patients with drug resistance to these drugs.

Key words: Sarcoma 45, Pliss lymphosarcoma, lymphocytic leukemia L1210, anticancer drugs, collateral sensitivity.

Drug resistance of tumors to various anticancer agents reduces the effect of treatment of oncological patients. At the same time, tumor cells may arise not only to a specific drug, but also to other compounds with different chemical structure and other mechanism of action. This phenomenon is called multiple drug resistance (MDR). Of undoubted interest to understand the mechanisms of MDR is the research of cross-resistance (CR). CR circle includes a large number of substances [1]. Therefore, the possibilities of drug treatment of malignant neoplasms are still very limited [2, 3]. In this regard, the present topical development is optimal mode of using drugs, doses and combinations of antineoplastic compositions to enhance their therapeutic effect and reduce the general toxicity effects on the body [4, 5], the search for potential antineoplastic drugs, particularly of natural origin [2, 6, 7].

In the experiments, new natural preparations such as alhidin, alnusidine, sodium salt of 1, 2-3-keto-18-dehydroglycyrrhetic acid (GA), leucoefdine and known compounds: platidiam, cyclophosphamide, sarcolysin, prospidin, nitrosomethylurea, 5-fluorouracil, 6-mercaptopurine, methotrexate, vincristine, adriamycin, rubomycin, and their combinations were used. Herbal preparations were administered daily, intraperitoneally: nitrosomethylurea (NMU) - once, other cytostatics - double with an interval of 96 hours in different doses. In the event of a change in their regimes and schemes of injection, the references in the notes of the corresponding figures were cited. To determine the nature of the interaction of drugs (potentiating or summation) [5, 8, 9], when combined, the smaller doses than in monotherapy were used.

The pharmacological effect of the drugs and their combinations on the growth of transplantable tumors of rats and mice was estimated by the coefficient of their growth inhibition (GI), the average life expectancy (ALE) and the extension of the life expectancy of animals (ELE). In the study of the general effect of drugs, the death of animals was taken into account.

A pronounced anticancer pharmacological effect with the resolving of tumors in 80% of rats was obtained using the combination of alhidin + platidiam + methotrexate in experiments with Pliss lymphosarcoma resistant to prospidin and rubomycin.

As a result, CR to Pliss lymphosarcoma in C 45 resistant to sarcolysin, and in Pliss lymphosarcoma resistant to rubomycin was overcome, the death of animals was not observed.

In control rats with Pliss lymphosarcoma resistant to rubomycin, the tumor was represented by cells of various sizes and shapes. The nuclei of cells are hyperchromic, pictures of mitosis are rare. Tumor tissue is poor in vessels and stroma. With the combined treatment (alhidin + platidiam + methotrexate) of this substrain, extensive necrosis and dystrophy of cells is observed. While using sarcolysin there was revealed the collateral sensitiveness in Pliss lymphosarcoma resistant to leucoefdine (with tumor resolving in 60% of rats). With a combination of sarcolysin and alhidine in half the maximum tolerated doses (> / MTD), a deep block of DNA synthesis was noted (synthesis suppression by 91.4-97.1%).

This combination, moreover, didn't reduce peripheral blood counts. While using another combination with alhidin (alhidin + prospidin + platidiam + cyclophosphamide) there was took away LR with cyclophosphamide on C 45 resistant to 5- fluorouracil, CR to Pliss lymphosarcoma resistant to prospidin and rubomycin, CR in platidiam to Pliss lymphosarcoma resistant to leucoefdine (with tumor resolving in 60% of rats).

A similar result for MDR was obtained when the combination (alhidin + platidiam + vincristine + adriamycin) was applied to LCP and its drug-resistant variants without side effects.

On C 45, resistant to 5-fluorouracil, a potentiating result was noted with the resolving of tumors in 60% of rats from combinations of alhidin + adriamycin; alhidin + vincristine and alhidin + 5-fluorouracil + adriamycin.

For this purpose, we used cyclophosphamide and NMU [10, 11] in combination with herbal preparations. NMUs have a fairly wide spectrum of action on human tumors, and their ability to pass through the blood-brain barrier is used to treat brain tumors and brain metastases, breast tumors, lung tumors and melanomas [10, 11]. They are also characterized by the absence of CR to anticancer agents from other classes. The promising results on the combined use of methyl and chloroethyl N-alkyl nitrosoureas (ANU) indicate the promise of using NMUs in the combined therapy of tumors [2] with the development of optimal regimens for the treatment of neoplastic diseases. This requires additional studies in animals with experimental tumors [4].

In this regard, we studied the effect of NMUs separately and in combination with plant compounds on drug-resistant C 45 variants and Pliss lymphosarcoma. NMU showed cross-resistance (CR) to all drug-resistant substrains, except C 45, resistant to prospidin and rubomycin.

The results of the treatment of tumors with a combined effect of half the MTD NMU with alnusidin, alhidin and MTD, as well as at intervals between the preparations (2, 4 and 24 hours) showed that the first interval (2 hours) was optimal. At the same time, there arises the overcoming of emerging drug resistance of C 45 to prospidin, 5-fluorouracil, and Pliss lymphosarcoma to prospidin and rubomycin (with resolving of tumors in 60% of rats, without side effects). The injection of the first NMU, and then herbal preparations reduces the antitumor activity and increases toxicity.

A morphological study of sarcoma 45 (spindle-cell sarcoma) resistant to 5-fluorouracil (95-generation without drug exposure) noted polymorphism of cells with hyperchromic nuclei. Cells form into bundles, randomly intertwining with each other. It is found in the tumor a lot of mitoses. The stroma is well developed and envelops cells in the form of thickened collagen fibers.

The histological picture of the cells of this strain during treatment with alhidine and nitrosomethylurea (with an interval of 2 hours) in comparison with the control showed a rarer distribution of small, pycnotic, polymorphic cells in tissue without a clear structure. Cells are non-compact. There are separate cells with hyperchromic nuclei. The foci of extensive necrosis are noted. There is a significant increase in connective tissue in the form of cords that enhance the anti-tumor effect of NMU and other chemotherapy drugs.

Similar data were obtained by us earlier with the combination of alhidin + vincristin + vinblastin with an interval of 2 hours after the injection of alhidin to animals with K. Guérin and CSU. Apparently, alnusidin, by increasing the content of thyroid hormones, contributes to enhancing the effectiveness of chemotherapy for drug-resistant tumors. The mechanism of the therapeutic action of herbal preparations (alhidin, alnusidin, sodium salt of 1.2-3-keto-18-dehydroglycyrrhetic acid) in case of hypersensitivity may be due to a certain influence through changes in the immune-hormonal balance of the animal organism.

In addition, being antioxidants, they reduce the toxicity of cytostatics and contribute to ELE of animals [10]. The results obtained are consistent with the research of L.B. Gorbacheva et al. [10, 11]. While studying the combinations of 1-methyl-1-nitrosourea with 1,3-bis- (2-chloroethyl) -1-nitrosourea along with positive results, they observed an increase in the overall toxic effect of the drugs. In this regard, they suggested the expediency of searching for compounds among synthetic and natural bioantioxidants that can reduce toxic effects.

A high inhibitory pharmacological effect was obtained in the treatment of alkydine, alnusidine and leucoeftin in the combined treatment of the original mouse tumors. Alhidin and alnusidin in MTD have a significant inhibitory effect on cervical cancer and LL (60 and 73%, respectively, $P < 0.05$). These results are enhanced by combining them with 1/2 MTD and platidiam, vincristine, adriamycin, 5-fluorouracil. A moderate antitumor effect on these strains was obtained by the preparation of sodium salt of 1,2-3-keto-18-dehydroglycyrrite acid, both individually and in combination with the antitumor compounds mentioned.

In addition, we also studied the effect of herbal preparations (alhidin, alnusidine, sodium salt of 1,2-3-keto-18-dehydroglycyrrhetic acid) and their combinations with known cytostatics on lymphocytic leukemia P-388, L 1210 and its medicinal resistant options.

When exposed to alhidin, the ELE of animals reaches up to 90% with L 1210 resistant to nitrosomethylurea. The minimum activity of alhidine is noted on L 1210, the initial (up to 30% ELE) and its drug-resistant variant to methotrexate (up to 37% UPZH). Vincristine and platidiam moderately influenced the animals ELE on both the initial and drug resistant variants with L 1210. However, when exposed to the combination of alhidine with anticancer drugs, the ELE of animals with L 1210 increases: alhidine + vincristine -114% in experiments with a resistant variant to NMU; alhidin + platidiam in 1/2 MTD on resistant variants to methotrexate (117%), NMU (114%) and 6-mercaptopurine (134%). The therapeutic effect of the triple combination (alhidin + vincristine + cyclofosfan) at 1/2 MTD (ELE up to 209%) is stronger than double (alhidin + vincristine and alhidin + cyclophosphamide). Combinations of the four drugs (alhidine + vincristine + cyclophosphamide + platidiam) were less effective than of the three, apparently due to increased toxicity.

When treating alnusidine, the drug-resistant variants of L 1210 (up to 81% of ELE) in comparison with the initial (up to 33% of ELE) turned out to be more sensitive to it. The effects of 6-mercaptopurine, vincristine, platydiam, adriamycin were moderately sensitive to both the initial (up to 55% of ELE) and drug-resistant variants L1210 (up to 60% of ELE) compared with the effects of NMU (up to 122% of ELE).

ELE was noted up to 203% with the combination of alhidin + cyclophosphane + methotrexate in L 1210, resistant to NMU, and up to 152% to 6-mercaptopurine. A similar result was obtained from the triple combination (alhidin + vincristin + platidiam) on these strains (up to 193% of ELE) compared with double combinations. However, alnusidine + ELE + methotrexate in animals with the triple combination of animals in the comparison with the double (alnusidin + NMU) were not found, respectively. L 1210, resistant option to metrotrexate. However, no special changes in the ELE of animals with the triple combination alnusidine + HMM + methotrexate in comparison with double (alnusidine + NMU) were not found, although in both cases a significant (up to 131 and 127%, respectively) animals ELE with L 1210, resistant option to metrotrexate.

As it is known, vincristine is one of the components of the chemotherapy of hemoblastosis patients. Its antitumor efficacy is especially high in the treatment of acute lymphoblastic leukemia (ALL). Nevertheless, there are options for ALL, resistant to chemotherapy with vincrastine, and, conversely, variants of acute myeloblastic leukemia, which can be successfully treated with a combination of drugs, including vincristine. Despite the widespread clinical use of vinca-alkaloids, the mechanism of their antitumor action is still not clear. In connection with this, a number of authors have established that tumor cells and blood (mice and patients with hemablastosis) sensitive to vincristine are associated with a greater amount of the drug than are resistant to it [7, 12].

On the basis of literature and our own data, it can be assumed that the herbal preparations studied by us increase the accumulation of vincristine in the cells of the initial and, especially, drug-resistant variants.

The injection of the preparation of sodium salt of 1,2-3-keto-18-dehydroglycyrretic acid in the triple combination (sodium salt of 1,2-3-keto-18-dehydroglycyrrite acid + vincristine + cyclophosphamide) in

MTD was expressed by inhibitory effect on both the initial L 1210 (up to 160% ELE) and drug-resistant variants (up to 167% ELE). Individually, the preparation of sodium salt of 1,2-3-keto-18-dehydroglycyrrite acid is active with respect to only L 1210, resistant to 6-mercaptopurine (up to 77% of ELE), without toxic manifestations.

The results obtained correspond to the goal of modern chemotherapy of a number of tumor diseases [7], where there is a need not only to achieve clinical remission, but also to increase life expectancy [2.4].

It has been established that the three main principles of polychemotherapy (the activity of each of the drugs in a given tumor, the different mechanism of their action and the different nature of toxicity) cannot explain all the rational combinations, predict the doses of the combined means and the modes of their injection. To identify the correlation of side and antitumor effects of new drugs and their combinations in order to reduce toxicity and increase the therapeutic effect and to overcome cross-and multi-drug resistance, special experimental studies are needed.

Cross, multidrug resistance to known and new herbal preparations in experiments on rats with resistant substrains of Pliss lymphosarcoma and sarcoma 45, and mice with resistant lymphocytic leukemia L 1210 were noted. Collateral (or increased) sensitivity of drug-resistant substrains to the new herbal medicines is revealed.

Induced drug (acquired) resistance to known chemotherapy drugs is removed when they are combined with 2-3 plant compounds (alhidin, alnusidine, sodium salt 1.2-3-keto-18-dehydroglycyrrite acid) when changing the treatment regime and dose of drugs. Often, herbal preparations, without expressing antitumor activity, when combined with chemopreparations, reduce the pharmacotoxic and depressive effects on blood formation and the immune system of cytostatics. At the same time, a sharp suppression of DNA synthesis, a decrease in the content of SH-groups and some steroid hormones with an increase in the content of thyroid hormones in drug-resistant tumors.

Thus, cross-drug, multiple drug resistance, collateral or (increased) sensitivity to known anti-tumor substances in drug-resistant substrains of rats and mice have been established. Induced drug resistance is removed with the help of combinations of new natural herbal preparations with known antitumor compounds in the optimal variants of the reception regime, their combination, dose and synergy of their combinants.

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ТАБИҒИ ПРЕПАРАТТАРДЫ ЦИТОСТАТИКТЕРМЕН БІРІКТІРГЕН КЕЗІНДЕГІ ДӘРІГЕ ТҰРАҚТЫ ҚАТЕРЛІ ІСІКТЕРДІ ТЕЖЕУІ

Аннотация. Плисс лимфосаркомасы өсімдік және цитостатиктерге, ал саркома 45 тек химиопрепараттарға дәрілік тұрақтылық көрсетті. Плисс лимфосаркомасында, саркома 45, лимфолейкоз L1210 жаңа табиғи препараттарына және белгілі ісікке қарсы препараттарға айқаспалы, көпжақты тұрақтылық байқалады. Плисс лимфосаркомасында белгілі фармакопрепараттарға ал саркома 45, L1210 жаңа табиғи өсімдік препараттарына жоғарғы коллатералды сезімталдық анықталды. Плисс лимфосаркомасының, саркома 45, L1210 дәріге тұрақтылығын жаңа өсімдік қосылыстарымен немесе оларды ісікке қарсы синтетикалық препараттармен біріктіріп, біріктірілген заттардың мөлшерін және санын өзгерту арқылы жоюға болады. Табиғи препараттарына және оның белгілі цитостатиктермен біріктірілуінде нитрозометилмочевинаға және 6-меркаптопуринге тұрақты лимфоидты лейкемия L1210 сезімталдық көрсетті.

Тәжірибелік зерттеудің нәтижесінде табиғи отандық жаңа дәрілік препараттардың көмегімен бірнеше сағат бұрын (2 және 4) жоғары көтере алатын (жануарлар) мөлшерде пайда болған дәрілік тұрақтылықты жою үшін нитрозометилмочевина, платидиам және адриамицин дәрілеріне тұрақтылығы бар науқастарға енгізудің алдындағы клиникалық тиімділігін жоспарлау критериіне жатады.

Түйін сөздер: саркома 45, Плисс лимфосаркомасы, лимфолейкоз L1210, қатерлі ісікке қарсы препараттар, коллатералды сезімталдық.

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ПРОТИВООПУХОЛЕВОЕ ИНГИБИРОВАНИЕ ПРИРОДНЫХ ПРЕПАРАТОВ В СОЧЕТАНИИ С ЦИТОСТАТИКАМИ НА ЛЕКАРСТВЕННО-РЕЗИСТЕНТНЫЕ ОПУХОЛИ

Аннотация. Лекарственно-резистентные подштаммы лимфосаркомы Плисса устойчивы как к растительным, так и цитостатикам, а саркома 45 – только к синтетическим препаратам. Проявляется перекрестная, множественная резистентность как к новым природным, так и известным противоопухолевым препаратам у резистентных подштаммов лимфосаркомы Плисса, саркомы 45, лимфолейкозу L 1210. Выявлена коллатеральная чувствительность к известным химиопрепаратам у лекарственно-резистентных вариантов лимфосаркомы Плисса и к новым природным препаратам у резистентных подштаммов саркомы 45, L 1210. Индуцированная лекарственная резистентность лимфосаркомы Плисса, саркомы 45 и L 1210 снимается новыми растительными соединениями или их комбинациями с противоопухолевыми препаратами, изменяя дозы и количество комбинантов. Результаты экспериментальных исследований по преодолению возникшей лекарственной резистентности с помощью природных препаратов в 1/2 МПД за несколько (2 и 4) часов до начала лечения нитрозометилмочевиной, платидиамом и адриамицином служат критерием для прогнозирования клинической эффективности у больных с лекарственной резистентностью к данным препаратам.

Ключевые слова: саркома 45, лимфосаркома Плисса, лимфолейкоз L1210, противоопухолевые препараты, коллатеральная чувствительность.

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