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ANTITUMOR AND ANTIMETASTATIC EFFICIENCY OF ANTITUMOR VACCINE AND AMIXIN COMBINED ACTION IN MICE WITH LEWIS LUNG CARCINOMA

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The aim of the research was to investigate the possibilities of increasing the efficiency of auto vaccinotherapy through the use of the endogenous interferon inductor amixin in mice with Lewis lung carcinoma. An effective plan for use of tumor vaccine and amixin, administered orally (25 mg/kg) 3 hours before each of the five injections of the vaccine, was developed. Its use in mice with transplanted Lewis lung carcinoma significantly exceeded the results of the introduction of antitumor vaccine alone: tumor growth inhibition index respectively 54.59 ± 1.97 and 43.79 ± 0.96%, and the average lifespan of mice – 56.2 ± 2.06 and 47.0 ± 1.50 days. In animals with minimal residual tumor (after surgical removal of the primary tumor) in adjuvant mode of antitumor vaccines amixin was effective with the introduction of the latter in the dose 3 hour before the vaccine or after 1 day after each introduction. The frequency of metastasis decreased to 70%, the average number of metastases and their volume in 8.8 and 34.0 times in comparison with those operated control mice, when compared to similar data of mice who received only the vaccine and their respective indexes were reduced at 2.0 and 2.25 times. The index of inhibition of metastasis using a combined scheme was 92.6%, that of the vaccine alone 83.08%. Further determination of the mechanisms of synergistic effect antitumor vaccines and amixin will enable the use of different biopreparations and will help to develop effective schemes of therapy of cancer patients.

Key words: amixin, cancer vaccines, Lewis lung carcinoma.

According to current data, antitumor vaccines (AV) have high therapeutic efficiency if combined with adjuvants of various origin, and immune response inducing cytokines [1, 2]. Of particular scientific interest are the effects of interferon (IFN) relating to tumor's increasing immunogenicity and changing sensitivity to T-lymphocyte cytotoxicity. It was shown that IFN directly impacts tumor growth and differentiation, and induces apoptosis [3]. Thus it is necessary to study its role as part of combination with other biological agents. Results of experimental and clinical studies substantiate the use of IFN-α as an optimization element of complex treatment to reduce risks of metastasis and improve the quality of life for cancer patients [4, 5].

Discovery of the unique properties of IFN stimulated the search for substances activating the synthesis of endogenous IFN, so-called IFN inducers [6–8]. One of these is amixin (tilorone), oral low molecular weight inducer of endogenous IF, the which activity is related to the immunomodulatory properties [9–11]. Information on significant antitumor activity of amixin has been obtained in model tumor experimental studies, also in clinical trials in patients with melanoma, breast cancer, renal cell carcinoma [12, 13]. It has been shown that the combined use of antitumor drugs and amixin contributes to strengthening growth inhibition of model tumors, and reduces metastasis [10, 14, 15]. Particular attention is paid to studying effects of IFN combined with vaccinotherapy [4, 16, 17].

In our previous studies it has been found that the use of IFN or subalin (recombinant strain of probiotic bacteria *B. subtillis* 2335/105 with embedded gene of human IFN synthesis) significantly increases the efficiency of vaccinotherapy in case of transplanted model Lewis lung carcinoma (LLC) [18, 19].

The aim of present work is development of protocols of effective use of AV and inducer of endogenous IFN, amixin.

Materials and Methods

Mice of the line C57Bl (males 2.5 months, 20–22 g, bred in RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine) were used in experiments according to the International Animal Research Regulations.

To determine the antitumor efficiency of combined action of AV and amixin, mice were transplanted LLC in femoral muscle ($4.5 \cdot 10^5$ living tumor cells per mouse). The cellular suspension for transplantation was prepared according to method requiring preliminary tumor trypsinization. AV were prepared following [20] using tumor tissue and filtrate of culture liquid of *B. subtilis* B-7025. 0.3 ml of AV were injected intramuscularly 5 times at the 1st, 4th, 8th, 12th and 15th days after tumor grafting. Amixin was introduced orally at 10.0 and 25.0 mg/kg (0.2 and 0.5 mg in 0.2 ml respectively) exclusively (third and fifth groups) or as part of the combined scheme (second and fourth groups) three hours before PV injection. The first group was given only AV. The efficiency of autologous AV and amixin separately and combined was estimated by comparing common characteristics of LLC growth in control (sixth group) and experimental mice.

The tumor growth dynamics, animal survival and average life expectancy (ALE) were determined. Tumor growth inhibition (TGI) index was calculated as:

$$TGI = (Vc - Ve/Vc) \cdot 100\%,$$

where Vc and Ve are average tumor volume in control and experimental mice respectively.

At 7th, 14th and 21st day after LLC grafting, functional activity of peritoneal macrophages (Mph) was assessed by HCT-test, and levels of IgG to LLC antigens was determined in blood serum [21].

Antimetastatic action of the combined protocols of AV and amixin was studied in mice with minimum residual tumor disease. LLC was transplanted ($2.5 \cdot 10^5$ cells per mouse) into hind-limb cushion, and at the 19th day after that primary tumors were surgically removed in all mice (anesthetized by sodium thiopental 60 µml subcutaneously) by cutting off the ligature-bound distal part of affected limb (surgical removal, SR). Subsequently the experimental animals were vaccinated (5 times, 0.3 ml subcutaneously). Only the times of the first vaccination were different: mice of first, second and third groups were given AV at 1st, 4th, 7th, 10th, and 14th day after SR; mice of the fourth and fifth groups at the 4th, 7th, 10th, 13th, and 17th day after SR. Amixin was given *per os* (25 mg/kg; 0.5 mg per mouse in 0.25 ml), three hours before each AV injection (1st combined protocol; 2nd experimental group) or 24 hours after it (2nd combined protocol; 3rd and 5th experimental groups). Control mice were given similar doses of NaCl saline in same time after SR.

Antimetastatic effect was estimated at the 28th day after SR (47th day after LLC grafting) by quantity and volume indexes of metastases in lungs: frequency of metastasis (%); average number of metastases per mouse; average volume of a metastasis. Metastases inhibition index (MII) was calculated as follows:

$$MII = \frac{A_c \cdot M_c - A_e \cdot M_e}{A_c \cdot M_c} \cdot 100\%,$$

A_c and A_e — number of animals with metastases in control and experimental groups;
M_e and M_c — average number of metastases in animals of control and experimental groups.

Statistical analysis was performed according to common methods of variation statistics. Results are given as $M \pm m$, where M is arithmetic mean, m is standard error. Differences assessed as probable at $P < 0.05$.

Results and Discussion

According to analysis of LLC growth dynamics indexes (Fig. 1), the tumor growth is reduced in all animal groups who received AV and/or amixin. The least tumor volume is found in mice receiving AV and amixin in doses of 25 mg/kg (4th group). Average values of TGI index during 10th to 38th days after LLC transplantation in this group is $54.59 \pm 1.97\%$ (Table 1), significantly exceeding the results after only vaccinotherapy — $43.79 \pm 0.96\%$, ($P < 0.05$). As a trend it's better than combined use of 10 mg/kg AV and amixin, $49.24 \pm 1.73\%$ ($0.1 < P < 0.05$).

Table 1. **Average inhibition of LLC growth (10^{th}–38^{th} days) in mice treated with AV and/or amixin**

Group №	Group characteristics	TGI, % $M \pm m$	Significant difference between groups (*$P < 0,05$; **$0,1 < P < 0,05$):
1	AV	43.79 ± 0.96	2*, 3*, 4*
2	AV + amixin, 10 mg/kg	49.24 ± 1.73	1*, 3*, 4**, 5*
3	Amixin, 10 mg/kg	39.61 ± 0.83	1*, 2*, 4*, 5**
4	AV + amixin, 25 mg/kg	54.59 ± 1.97	1*, 2**, 3*, 5*
5	Amixin, 25 mg/kg	42.14 ± 0.88	2*, 3**, 4*

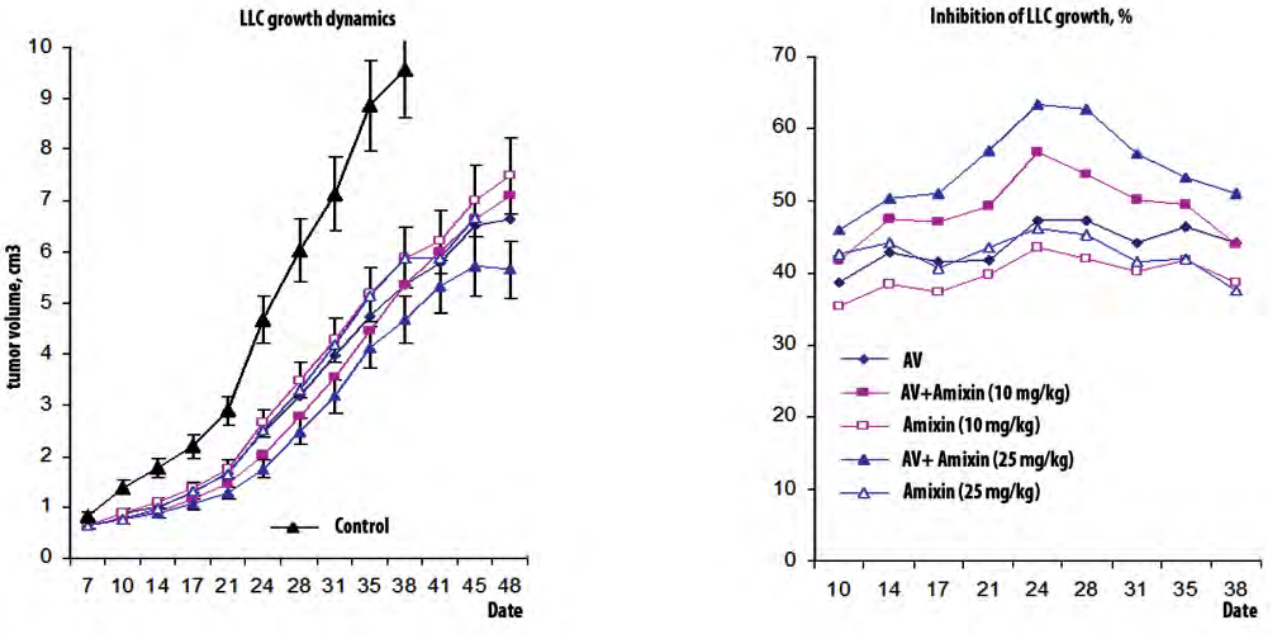

Fig. 1. **Characteristics of Lewis lung carcinoma in mice treated with AV and/or amixin**

It should be noted that the results of implementation of both combined plans (AV and amixin, 10 mg/kg and 25 mg/kg) significantly exceed the effects of separate treatments by AV or similar doses of amixin ($P < 0.05$). LLC growth inhibition in experimental animals occurs together with better survival indexes than in control (Fig. 2). The advantages of combined use of AV and amixin in doses of 25 mg/kg are obvious: mortality in animals of this group is observed in 47^{th} to 70^{th} days while all control mice died before the 40^{th} day.

ALE of animals with transplanted LLC who received AV and/ or amixin significantly exceeds that of the control group (32.87 ± 1.89 days, $P < 0.05$) (Table 2). The best results are observed for combined use of AV and amixin in doses of 25 mg/kg (56.2 ± 2.06 days) — ALE of these mice is 70.98% higher than that of the control group, and is quite different from ALE of mice given only AV or amixin in that dose (47.0 ± 1.50 and 43.5 ± 1.55 days respectively). The combined plan with amixin in doses of 10 mg/kg was significantly inferior in this regard.

Analysis of functional activity of peritoneal Mph in HCT-test at the 7^{th}, 14^{th}, and 21^{st} day (Table 3) shows no significant difference in mice indexes of this group compared to the tumor growth control (TGC). But evaluating the levels of IgG to LLC antigens in BS in mice given AV and amixin in doses of 25 mg/kg after injections reveals the highest value among all experimental groups: at the 7^{th} day after transplantation it is 1.732 ± 0.007 optical units, significantly exceeding IgG levels in control mice (0.747 ± 0.011 optical units, $P < 0.05$). Later after transplantation (21^{st} day), IgG levels in BS of animals of all

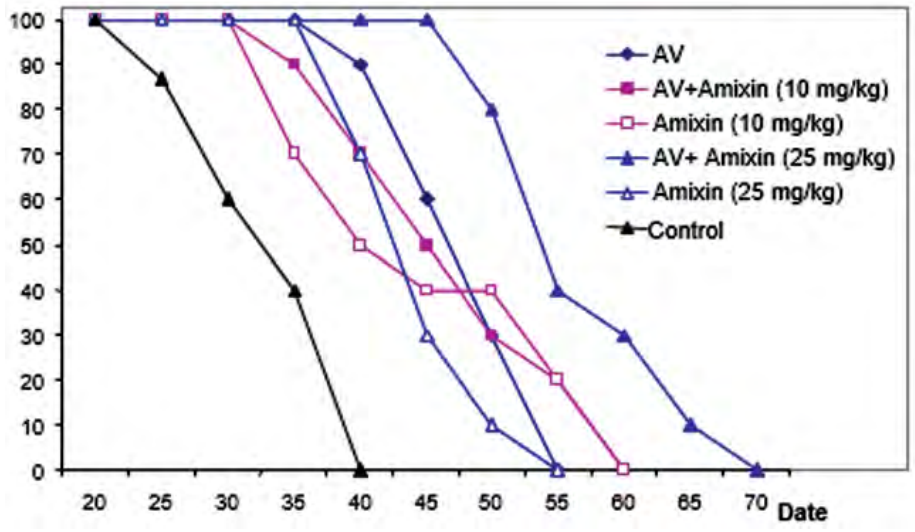

Fig. 2. **Survival in mice (%) with Lewis lung carcinoma after treatment with AV and/or amixin**

Table 2. **Average life expectancy in mice with Lewis lung carcinoma after treatment with AV and/or amixin**

Group №	Group characteristics	ALE			Difference between groups (*$P < 0.05$)
		$M \pm m$	t	IM, %	
1	AV	47.0 ± 1.50	6.72*	+42.99	4, 6
2	AV + amixin, 10 mg/kg	45.9 ± 2.75	4.64*	+39.64	4, 6
3	Amixin, 10 mg/kg	43.7 ± 2.98	3.66*	+32.95	4, 6
4	AV + amixin, 25 mg/kg	56.2 ± 2.06	9.71*	+70.98	1, 2, 3, 5, 6
5	Amixin, 25 mg/kg	43.5 ± 1.55	4.99*	+32.34	4, 6
6	Tumor growth control (TGC)	32.87 ± 1.89			1, 2, 3, 4, 5

Note: * — $P < 0.05$ compared to TGC.

groups is similar to that of intact mice (0.656 ± 0.010 optical units) excepting the group given AV and amixin (25 mg/kg) with higher IgG levels (0.969 ± 0.014 optical units, $P < 0.05$).

Thus, in mice with LLC, AV is more efficient if combined with endogenous IFN inducer, amixin, in doses of 25 mg/kg. Inhibition of tumor growth is 54.59 ± 1.97%, ALE compared to TGC is longer by +70.98% ($P < 0.05$), exceeding same indexes in mice given only AV. In mice with combined treatment, during the later tumor growth (40th day), lower IgG to LLC antigens and circulating immune complexes level (CIC) is found which points to favorable prognosis of the disease.

In another experiment, antimetastatic activity of combined AV and amixin (in doses of 25 mg/kg) in C57Bl mice with LLC is studied. The results of analysis of quantitative characteristics of metastasis at the 28th day after SR show significant difference in the respective values for experimental and control mice. First of all it should be noted that metastasis occurs in lungs of 100% control mice; in 80% mice given only AV regardless of the time of first vaccination (1st and 4th groups); 70% mice of both combined plans of AV and amixin if AV is injected in 24 hours after SR (Table 4). Combined plan with vaccination starting 72 hours after SR shows results similar to that of only using AV (80%).

As for the index of average number of metastasis per mouse, the least values are found in both combined plan groups if AV were injected 24 hours after SR (1.60 ± 0.37; 2nd and 3rd groups), which is significantly different from vaccination alone (3.20 ± 0.66;

Table 3. **Levels of oxygen-dependent bactericide activity of peritoneal Mph and IgG to LLC antigens in blood serum of mice given AV and/or amixin**

Group characteristics	Activity level of Mph in HCT-test, optical unit			IgG level, optical unit		
	7^{th} day	14^{th} day	21^{st} day	7^{th} day	14^{th} day	21^{st} day
AV	0.74 ± 0.05*	0.42 ± 0.01*	0.40 ± 0.01	1.09 ± 0.03*	0.77 ± 0.02	0.73 ± 0.01
AV + amixin, 10	0.40 ± 0.01	0.32 ± 0.02	0.43 ± 0.01*	0.77 ± 0.02	1.02 ± 0.33	0.60 ± 0.03
Amixin, 10	0.47 ± 0.01	0.40 ± 0.01*	0.37 ± 0.02	0.10 ± 0.01*	0.79 ± 0.03	0.75 ± 0.04
AV + amixin, 25	0.52 ± 0.03	0.40 ± 0.01*	0.41 ± 0.01	1.73 ± 0.02*	0.95 ± 0.01	0.97 ± 0.02*
Amixin, 25	0.37 ± 0.01*	0.35 ± 0.01	0.45 ± 0.02	0.67 ± 0.02	1.41 ± 0.02*	0.65 ± 0.01
TGC	0.51 ± 0.01	0.34 ± 0.01	0.37 ± 0.01	0.75 ± 0.03	0.86 ± 0.03	0.65 ± 0.01
Intact control	–	–	–	0.66 ± 0.01	0.68 ± 0.02	0.63 ± 0.01

Note: * — significant difference with respective value in TGC group ($P < 0.05$).

Table 4. **Number of metastases in mice with LLC treated with combined AV and amixin after removal of primary tumor**

Group №	Group characteristics	Mice with metastases (%)	Total number of metastases	Average number of metastases per mouse		MII, %
				$M \pm m$	*$P < 0.05$; **$0.01 < P < 0.05$ between the groups	
1	AV (1^{st}–14^{th} days)	80.0	32	3.20 ± 0.66	2*; 3*; 4**; 5*; 6*	83.08
2	AV (1^{st}–14^{th} days) + amixin (1^{st} plan)	70.0	16	1.60 ± 0.37	1*; 4*; 5*; 6*	92.60
3	AV (1^{st}–14^{th} days) + amixin (2^{nd} plan)	70.0	16	1.60 ± 0.37	1*; 4*; 5*; 6*	92.60
4	AV (4^{th}–17^{th} days)	80.0	29	5.80 ± 1.59	1**; 2*; 3*; 6*	69.33
5	AV (4^{th}–17^{th} days) + amixin (2^{nd} plan)	80.0	38	7.60 ± 2.01	1*; 2*; 3*; 6*	59.81
6	Control	100	227	14.10 ± 0.67	1*; 2*; 3*; 4*; 5*	–

1^{st} group). If vaccination started 72 hours after SR, average number of metastases grows both in vaccine-only treatment and in combined use with amixin (5.80 ± 1.59 and 7.60 ± 2.01; 4^{th} and 5^{th} groups) but in the latter case the difference between the groups is not statistically significant. On the whole, the number of metastases decreases in all experimental groups compared to control (14.10 ± 0.67; $P < 0.05$), as can seen from the high values of MII.

If the vaccination started 24 hours after SR, MII is 92.6% in both cases of combined use of AV and amixin, and this is significantly higher than in case of vaccination only (83.08%). If vaccination started 72 hours after SR, MII in mice given only AV is reduced to 69.33%; in mice given combined treatment (plan 2) to 59.81%. The results mean that the combined use of AV and amixin exhibits better antimetastatic activity if vaccination started earlier (24 hours) after SR, since delaying the treatment by AV and amixin for 96 hours reduces the antimetastatic effect. The observed particularities are confirmed by studying volume characteristics of metastasis (Table 5).

Significant reduction of average volume of metastases is recorded in all vaccinated

Table 5. **Metastasis volume in mice with LLC after removal of primary tumor and treatment by combined AV and amixin**

Group №	Group characteristics	Average metastasis volume per mouse		Average volume of a metastasis	
		$M \pm m$	$P < 0.05$ with groups	$M \pm m$	$P < 0.05$ between the groups
1	AV (1^{st}–14^{th} days)	72.85 ± 25.70	5; 6	22.77 ± 5.59	5; 6
2	AV (1^{st}–14^{th} days) + amixin (1^{st} plan)	40.04 ± 10.57	4; 5; 6	25.02 ±6.48	5; 6
3	AV (1^{st}–14^{th} days) + amixin (2^{nd} plan)	32.19 ± 9.46	4; 5; 6	20.12 ± 6.17	5; 6
4	AV (4^{th}–17^{th} days)	147.91 ± 41.42	2; 3; 6	25.50 ± 3.62	5; 6
5	AV (4^{th}–17^{th} days) + amixin (2^{nd} plan)	377.26 ± 128.41	1; 2; 3; 6	49.64 ± 6.03	1, 2, 3, 4, 6
6	Control	1121.0 ± 59.81	1, 2, 3, 4, 5	74.63 ± 4.46	1, 2, 3, 4, 5

mice compared to control: 72.85 ± 25.70; 40.04 ± 10.57; 32.19 ± 9.46; 147.91 ± 41.42 and 377.26 ± 128.41 mm^3 (in the 1^{st}–5^{th} groups respectively) and 1121.0 ± 59.81 mm^3 in control mice. The least values are observed in both combination plans (2^{nd} and 3^{rd} groups) but the differences with the value for the mice given only AV (1^{st} group) are not significant ($P > 0.05$). The difference in values is significant for the 3^{rd} and 5^{th} mice groups, given combined AV and amixin according to the plan 2 (amixin 24 hours after each of the five vaccinations) but with different times of first vaccination — 32.19 ± 9.46 and 377.26 ± 128.41 mm^3 ($t = 3.91$; $P < 0.05$), supporting the importance of early start of vaccination after SR.

Analysis of average metastasis volume shows practically same results in mice of the 1^{st}–3^{rd} groups given only AV or in combination with amixin (22.77 ± 5.59; 25.02 ± 6.48; 20.12 ± 6.17 mm^3); similar findings are observed for mice of the 4^{th} group given only AV 96 hours after SR (25.50 ± 3.62 mm^3). But all those results significantly differ from these of mice of the 5^{th} (49.64 ± 6.03 mm^3) and control (74.63 ± 4.46 mm^3) groups, supporting the importance of timely early beginning of combined treatment by AV and amixin to achieve high antimetastatic efficiency.

Thus, pronounced antimetastatic activity of two plans of combined action of autologous AV and amixin given *per os* in doses of 25.0 mg/kg (0.5 mg per mouse) three hours before AV injection or 24 hours after, is observed in experiment on model LLC with surgical removal of primary tumor. There is no significant difference between results for these two combined plans according to quantitative and volume characteristics of metastasis for considered indexes.

Significant advantages in using combined plans of vaccination and amixin over only vaccination is shown for the average number of metastasis and metastasis inhibition index (84.11% and 92.06%). All considered indexes support the importance of timely introduction of combined plan of autologous AV and amixin, that is early after tumor removal (in 24 hours). The results are the basis for increasing the vaccinotherapy efficiency using the inducer of endogenous IFN.

Thus, efficient plan of combined use of AV and inducer of endogenous IFN, amixin, is developed: *per os* introduction of amixin in doses of 25 mg/kg three hours before each of the five AV vaccinations. In mice with transplanted LLC the plan is more successful than only AV vaccinotherapy — tumor growth inhibition index is 54.59 ± 1.97 and 43.79 ± 0.96% respectively, and ALE of mice is 56.2 ± 2.06 and 47.0 ± 1.50 days respectively ($P < 0.05$).

In mice with residual tumor disease (after surgical removal of the primary tumor), adjuvant using of AV and amixin is effective in case the latter is introduced (in doses of 25 mg/kg) three hours before or 24 hours after each vaccination. AV and amixin combined result in frequency of metastasis 70%, average number of metastasis reduced to 1.60 ± 0.37 and metastatic volume reduced by 32.19 ± 9.46 mm^3 compared to analogous characteristics in control mice ($P < 0.05$). The IIM is in these conditions 92.6%.

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ПРОТИПУХЛИННА ТА АНТИМЕТАСТАТИЧНА ЕФЕКТИВНІСТЬ КОМБІНОВАНОЇ ДІЇ ПРОТИПУХЛИННОЇ ВАКЦИНИ ТА АМІКСИНУ У МИШЕЙ ІЗ КАРЦИНОМОЮ ЛЕГЕНЬ ЛЬЮЇС

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Метою роботи було дослідити можливості збільшення ефективності автовакцинотерапії за рахунок використання індуктора ендогенного інтерферону аміксину у мишей із карциномою легень Льюїс. Розроблено ефективну схему застосування протипухлинної вакцини та аміксину, яка полягає в пероральному введенні аміксину (25 мг/кг) за 3 год до кожного з п'яти введень вакцини. Застосування її у мишей із перещепленою карциномою легень Льюїс вірогідно перевищує результати введення протипухлинної вакцини в монорежимі — індекс гальмування пухлинного росту становить відповідно 54,59 ± 1,97 і 43,79 ± 0,96%, а середня тривалість життя мишей — 56,2 ± 2,06 і 47,0 ± 1,50 діб. У тварин з мінімальною залишковою пухлинною хворобою (після хірургічного видалення первинної пухлини) використання в ад'ювантному режимі протипухлинної вакцини з аміксином було ефективним за введення останнього в зазначеній дозі за 3 год до або через 1 добу після кожного її введення. Частота метастазування зменшувалась до 70%, середня кількість метастазів та їх об'єм — у 8,8 і 34,0 раза порівняно з відповідними показниками оперованих контрольних мишей, у разі зіставлення з аналогічними показниками мишей, що одержували тільки вакцину, — в 2,0 і 2,25 раза. Індекс інгібування метастазування за використання комбінованої схеми становив 92,6%, вакцини у монорежимі — 83,08%. Подальше визначення механізмів синергічної дії протипухлинної вакцини та аміксину дасть змогу застосовувати різні біопрепарати та сприятиме розробленню ефективних схем терапії онкохворих.

Ключові слова: аміксин, протипухлинна вакцина, карцинома легень Льюїс.

ПРОТИВООПУХОЛЕВАЯ И АНТИМЕТАСТАТИЧЕСКАЯ ЭФФЕКТИВНОСТЬ КОМБИНИРОВАННОГО ДЕЙСТВИЯ ПРОТИВООПУХОЛЕВОЙ ВАКЦИНЫ И АМИКСИНА У МЫШЕЙ С КАРЦИНОМОЙ ЛЕГКИХ ЛЬЮИС

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Целью работы было исследовать возможности усиления эффективности аутовакцинотерапии за счет использования индуктора эндогенного интерферона амиксина у мышей с карциномой легких Льюис. Разработана эффективная схема использования противоопухолевой вакцины и амиксина, которая заключается в пероральном введении амиксина (25 мг/кг) за 3 ч до каждого из пяти введений вакцины. Ее применение у мышей с перевиваемой карциномой легких Льюис достоверно превышает результаты введения противоопухолевой вакцины в монорежиме — индекс торможения опухолевого роста составляет соответственно 54,59 ± 1,97 и 43,79 ± 0,96%, а средняя продолжительность жизни мышей — 56,2 ± 2,06 и 47,0 ± 1,50 суток. У животных с минимальной остаточной опухолью (после хирургического удаления первичной опухоли) использование в адъювантном режиме противоопухолевой вакцины с амиксином было эффективным при введении последнего в указанной дозе за 3 ч до или через 1 сутки после каждого ее введения. Частота метастазирования уменьшалась до 70%, среднее количество метастазов и их объем — в 8,8 и 34,0 раза по сравнению с соответствующими показателями оперированных контрольных мышей, при сопоставлении с аналогичными показателями мышей, получавших только вакцину, — в 2,0 и 2,25 раза. Индекс ингибирования метастазирования при использовании комбинированной схемы составил 92,6%, вакцины в монорежиме — 83,08%. Дальнейшее определение механизмов синергического действия противоопухолевой вакцины и амиксина даст возможность применять различные биопрепараты и будет способствовать разработке эффективных схем терапии онкобольных.

Ключевые слова: амиксин, противоопухолевая вакцина, карцинома легких Льюис.