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THE CHEMOIMMUNOTHERAPY BASED ON DENDRITIC CELLS AND CISPLATIN IN EXPERIMENT

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The aim of the study was to develop a scheme of combined chemoimmunotherapy and to investigate antitumor and immunomodulatory activity of chemoimmunotherapy regimen using the vaccine based on dendritic cells and low-doses of cisplatin in CBA mice with sarcoma-37. Maximal antitumor and immunomodulatory effects were observed after application of the vaccine based on dendritic cells in combination with doses of cisplatin concentration of 2 mg/kg. Among significant immunomodulatory effects of combination therapy it has to be noted the increased functional activity of natural immunity, in particular, enhancing of cytotoxic activity of natural killer cells and the ability of peritoneal macrophages, neutrophils and spleen macrophages to increase their absorbing activity and to produce the active oxygen forms. The obtained results prove the expediency of combining of chemo- and immunotherapeutic methods for the development of more effective approaches to prevent recurrence and metastasis after primary treatment of cancer patients.

Key words: sarcoma-37, vaccine based on dendritic cells, cisplatin, chemoimmunotherapy.

Inefficiency of traditional methods of treatment of cancer patients forces the search of new approaches. Nowadays immunotherapy is considered as such a way and its sufficiency has been proved [1, 2]. Recently new types of immunotherapy have been investigated. Modern international standards of tumor immunotherapy consist of:

- multimodal approaches, which make simultaneous influence on different parts of immune system;
- usage of polyvalent antigen, that includes wide spectrum of tumor-associated antigens;
- reducing of impact or eliminating of factors which suppress the immune response, in particular, the number and functional activity of T-regulatory (T-reg) lymphocytes [3,4].

One of such new approaches is chemo-immune therapy (CIT), which implies the usage of low doses of chemical preparations and antitumor immunotherapy, in particular, antitumor vaccine on the base of dendritic cells (DC) [5, 6].

Nowadays the mechanisms of CIT influence on the cancer patients and on the tumor itself are not completely investigated. The standard

protocols concerning CIT usage during the treatment of cancer patients are not elaborated. It was established that low doses of chemical preparations make essential influence on tumor microenvironment due to their antiangiogenic effect, particularly thanks their cytotoxic effect on proliferating endotheliocytes of tumor vessels [17]. It was also shown that the usage of above mentioned low doses leads to the decrease of T-reg population with phenotype CD4⁺CD25⁺Fox P3⁺. These lymphocytes possess immunosuppressor ability which may enhance antitumor effect of the vaccine [9]. Hence, the elaborating of efficient scheme of CIT is a focal problem of modern oncology.

The aim of this investigation was to elaborate the scheme of combine CIT on the base of DC-vaccine and low doses of cisplatin in experiment and to study both: the influence of this vaccine on the growth of transplantable tumor and the state of immune system of tumor-bearing mice.

Materials and Methods

Fifty rat males of line CBA weighing 18–22 g, aged of 1.5–2 months were used

for the experiment. Rats were housed in an animal care facility of National Cancer Institute, Ukraine. All procedures with animals were performed in accordance with the principles of humanity as it was written in "General principles of animal experimentation" approved by the National Congress on Bioethics (Kyiv, 2001–2007) and in accordance with Council directive of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC).

Tumor cell line sarcoma-37 (S-37) was used as an experimental tumor model. Cells were injected intramuscularly in concentration of $2 \cdot 10^6$ cells per animal. Cisplatin was injected intraperitoneally, in doses of 0.2 mg/kg or 2 mg/kg. DC vaccine was injected intravenously into orbital sinus eyes in concentration of $0.2 \cdot 10^6$ DC per animal. The vaccination was carried out 3 times with the 3–4 day period between the injections; the start was on days 15 or 23 after tumor transplantation. The scheme of experiments with the usage of CIT is presented on Fig. 1.

All experimental animals were divided into such groups:

- control group (animals bearing S-37);
- DC 1 (animals bearing S-37, treated only with DC vaccine on days 15, 18 and 21 after tumor transplantation);
- DC 2 (animals bearing S-37 treated only with DC vaccine on days 23, 26 and 30 after tumor transplantation);
- CP 1 (animals bearing S-37 treated with cisplatin in dose of 0.2 mg/kg on days 7, 8, 9, 10 and 11 after tumor transplantation);
- CP 2 (animals bearing S-37 treated with cisplatin in dose of 2 mg/kg on days 7, 10, 13, 16 and 19 after tumor transplantation);

– CIT 1 (animals bearing S-37 treated with both: DC vaccine on days 15, 18 and 21 after tumor transplantation and cisplatin in dose of 0.2 mg/kg on days 7, 8, 9, 10 and 11 after tumor transplantation);

– CIT 2 (animals bearing S-37 treated with both: DC vaccine on days 23, 26 and 30 after tumor transplantation and cisplatin in dose of 2 mg/kg on days 7, 10, 13, 16 and 19 after tumor transplantation).

The experiment was carried out in the measurement of tumor volume in three planes at intervals of 2–3 days and its volume was determined by the formula:

$$V = 0.52 D^3,$$

where V is a tumor volume, 0.52 is a coefficient, D is a tumor diameter measured in mm.

On day 35 after tumor transplantation animals were devitalized and biomaterial was taken for further immunological investigations.

DC vaccine obtaining. Splenocytes of intact syngenic mice were used as a source of DC. Dendritic cells were purified according to [10] with some modification. All procedure with cells was performed in accordance with aseptic rules. Splenocyte suspension ($5 \cdot 10^6$ cells per ml) was incubated in RPMI-1640 medium at 37 °C and 5% CO₂ for one day. The cells were concentrated by centrifugation in 14.5 metrizamide density gradient at 1,000 rpm/min for 15 minutes. Dendritic cells were "charged" with tumor antigen by the following way: $1 \cdot 10^6$ cells per ml was incubated in RPMI-1640 medium at 37 °C and 5% CO₂ for four hours in the presence of mechano-chemically activated liophilized tumor cells in concentration of 10 mg per kg. Then DC were washed, the final concentration of cells was regulated till 1×10^6 cells per ml and final preparation was used as DC vaccine.

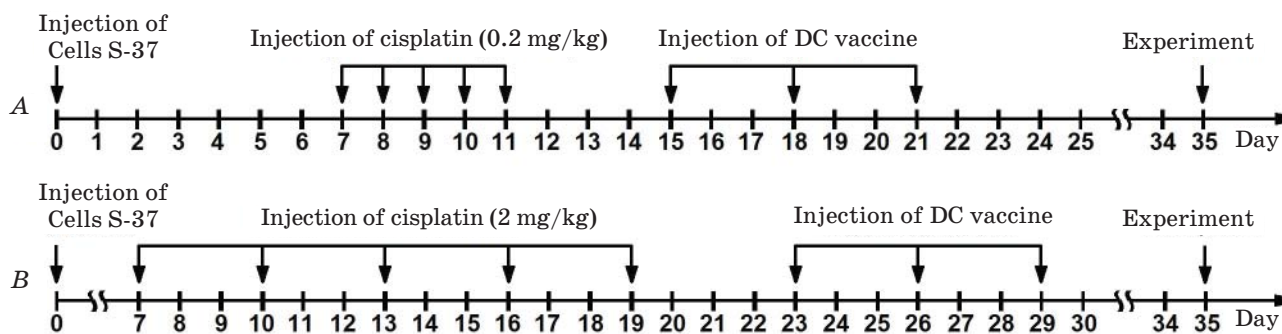


Fig. 1. Experimental scheme:

- A — scheme CIT with the usage of cisplatin in dose of 0.2 mg/kg and DC vaccine;
 B — scheme CIT with the usage of cisplatin in dose of 2 mg/kg and DC vaccine

Immunological essays. The number of activated spleen lymphocytes in certain populations was determined with the usage of flow cytometry method and monoclonal antibodies (Mc Ab), anti-CD 69, -CD54 FITC (BD, USA).

Functional activity of natural killer cells (NKC) and cytotoxic T-lymphocytes (CTL) was estimated using the flow cytometer. Lymphoma of mice OH-1, which was obtained from transplanted lymphoma induced by B.megaterium, served as the source of non-specific target cells. Cell line C-37 was used as the source of specific target cells.

Absorbing activity of peritoneal macrophages and splenocytes was measured by flow cytometry estimating the number of splenocytes which absorbed FITC-labeled bacteria *S. aureus* [11].

The ability of phagocytes to produce active oxygen forms (AOF) was established by flow cytometry detecting fluorescent compound (green spectrum domain) produced due to reaction between dihydrorhodamine 123 (DHR 123) with hydrogen peroxide and peroxyxynitrite. According to the obtained results the markers of spontaneous and stimulated fluorescence were determined and a coefficient of stimulation ($k = \text{stimulated fluorescence} / \text{spontaneous fluorescence}$) was calculated separately for neutrophils and monocytes [11].

All flow cytometry analyses were carried out with the usage of FACS Calibur (BD, USA) which had two laser installation ($\lambda = 488 \text{ nm}$ and $\lambda = 625 \text{ nm}$). The program Cell Quest-PRO was used to collect and analyze the data. Statistical treatment of the data was performed using Student t-test for parametric data and the Mann-Whitney test for nonparametric data.

To determine the volume of the primary tumor ANOVA was used for repeated measurements.

The studies were carried out in the framework of the research work of National Cancer State Institute according to the topic "To develop the method of specific and nonspecific immunotherapy in the experiment and to determine the indications for use for complex treatment of cancer patients." (BH.14.01.07.122-10, state registration number 010U002206, 2010–2012 yy.)

Results and Discussion

As the obtained results showed, the maximal antitumor effect was observed in case of CIT 2 when we used cisplatin in dose of 2 mg/kg and DC vaccine (Fig. 2). The tumor volume in this group was significantly decreased as compared with the control group of animals ($P = 0.001$) and the group of DC 2 ($P = 0.007$).

The usage of CIT 1 scheme didn't lead to the significant decrease of the primary tumor volume as compared with the control group and the animals which were treated with DC vaccine only (DC 1 group).

When cisplatin was singly used in dose of 0.2 mg/kg and 2 mg/kg (CP1 and CP2) the decrease of primary tumor volume was also observed as compared with the control group ($P = 0.012$ and $P = 0.011$ respectively)

It is known that chemotherapy not only promotes the elimination of regulatory suppressor cells, but also leads to certain negative effects e.g. it can suppress the functional state of the immune system. So, to develop the most effective scheme of combined CIT and to behind recommendations for clinical usage we investigated the state of the immune system of tumor-bearing animals after combined CIT.

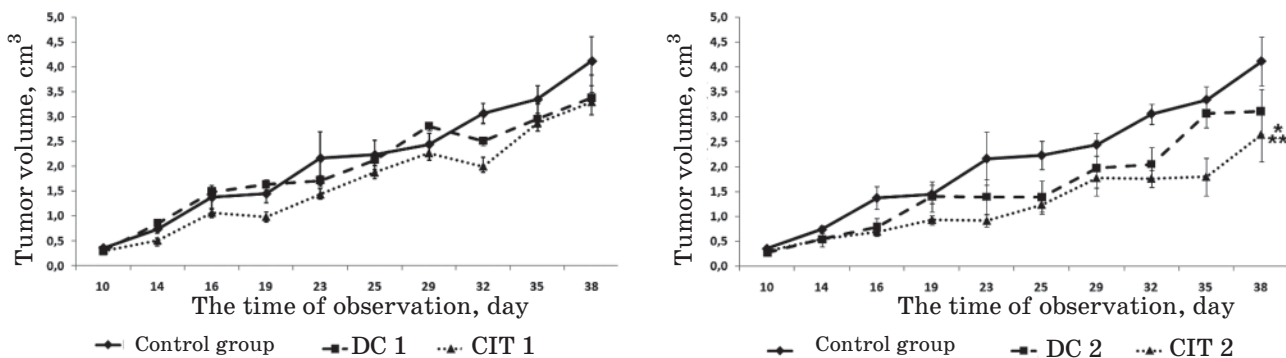


Fig. 2. The tumor volume of CBA mice with S-37, which were treated with combined CIT (* — $P < 0.01$ as compared with the control group; ** — $P < 0.01$ as compared with DC 2 group)

Antitumor immune response depends on the functioning both: the natural immunity (macrophages and NKC) and specific one (CTL and plasmatic cells). Taking into consideration above mentioned we investigated the cytotoxic activity (CA) of T-lymphocytes concerning specific target cells S-37 and CA NKC concerning nonspecific tumor cells OH-1.

The animals treated by combined therapy in accordance to CIT 2 had the increased level of cytotoxic activity by 37.4% concerning target cells OH-1 as compared with the control group ($P = 0.011$, Fig. 3). The significant increase of CA was observed at the animals treated by the therapy in accordance to CIT 1-by 33% as compared with the control group ($P = 0.035$). The usage of therapy in accordance to DC1 led to the increase of CA by 35% as compared with the group of untreated animals. We didn't observe any significant increase of CA level at the other group of animals during the cultivation of splenocytes with target cells OH-1.

So, the most pronounced increase of CA of splenocytes concerning target cells OH-1 was observed in the group of animals treated according to CIT-2.

Interaction of effector cells with target cells S-37 led to significant increase of CA (by 43.8%) in the groups of animals treated according to CIT 1 ($P = 0.035$). There was not significant increase of CA of splenocytes at the other groups.

It is known that antigen CD 69 is the early marker of lymphocyte proliferation. So, in

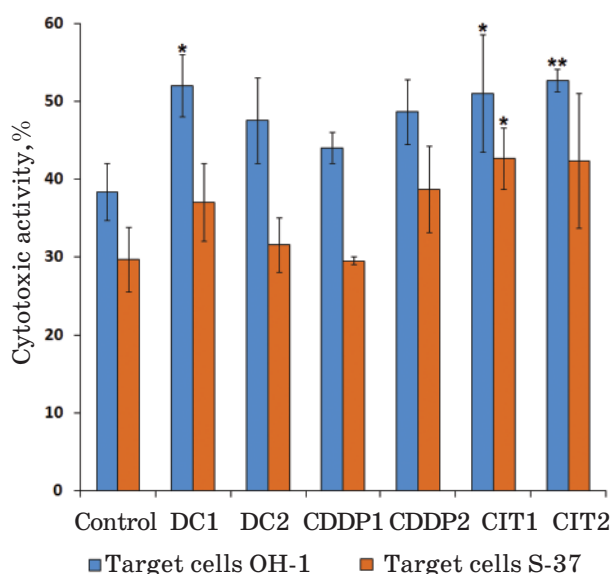


Fig. 3. Cytotoxic activity of splenocytes from CBA mice at the interaction with tumor target cells:

* — $P < 0.05$;

** — $P < 0.025$ as compared with the control group

our further investigation we determined the level of the expression of this antigen on the spleen surface of mice. It was shown that the amount of CD69⁺ spleen cells was increased at the animals treated according to CIT 1, CIT 2, CP1 and CP2. The amount of CD69⁺ cells was increased in 4 times at the animals treated by combined therapy according to CIT 1 ($P = 0.05$). The amount of CD69⁺ cells was increased in 3.5 times at the animals treated according to CP 1 ($P = 0.003$) and in 5.2 times at the animals treated according to CP 2 ($P = 0.033$) as compared with the control group. However, during the therapy according to DC 1 and DC2 we didn't observe any significant changes in amount of CD69⁺ spleen cells. On the base of the obtained results we can suggest that the usage of cisplatin low doses leads to the increase of the amount of CD69⁺ spleen cells by the elimination of immune system cells with suppressor abilities. This makes antitumor efficiency of DC vaccine more pronounced.

The ability of cells to diapedesis was determined via CD 54 (I-CAM-1) expression on the spleen surface. It is shown I-CAM-1 expression on the surface of T-, B-lymphocytes, macrophages and DC. Binding to LFA, which is expressed on the surface of endotheliocytes, the above mentioned I-CAM-1 promotes cell penetration from blood stream into inflammation place [12]. Using the combined therapy according to CIT 2 we noticed the increase of cells expressing CD 54 by 28% as compared with untreated animals ($P = 0.048$). However, there was not significant increase of CD 54 positive cells on the spleen surface as compared with the control group. The increased level of leukocytes expressing CD 54 proves their ability to penetrate through endothelium at the inflammation sites, where effector functions of these cells are realized.

Absorbing activity of peritoneal macrophages, neutrophils and monocytes is an important characteristic of natural antitumor and about infectious immunity [13, 14]. We didn't notice negative influence of cisplatin on the absorbing activity of phagocytes we even observed the strengthening of this function. At the animals treated by cisplatin in dose of 2 mg/kg (CP2) the absorbing activity of peritoneal macrophages was increased by 51.2% ($P = 0.016$) and by 154.0% in case of spleen macrophages ($P = 0.022$) as compared with the group of untreated animals ($P = 0.016$).

We noticed the increase of absorbing activity of peritoneal macrophages at the groups with combined therapy, in case of CIT 1 the absorbing activity was increased by 36%

($P = 0.02$) and , in case of CIT 2 this activity was increased by 62% ($P = 0.025$) as compared with the control group (Fig. 4).

We didn't observe the significant changes in absorbing activity of peritoneal macrophages at the other groups.

We could also notice the significant increase of neutrophile absorbing activity in the group CIT 2. The absorbing activity of neutrophiles in this group increased by $52.33\% \pm 4.67\%$ as compared with the control group, $37 \pm 5.29\%$ ($P = 0.04$). In the other groups of animals the significant changes of neutrophile absorbing activity were not observed. The absorbing activity of splenocyte fraction, which is identical to monocytes according to morphological characteristics, was significantly increased in groups of DC and CDDP2 (monotherapy), and in the groups of combined therapy as compared with untreated animals. The most pronounced increase of absorbing activity was observed in case of CIT 2, where it was increased in 3.7 times as compared with untreated animals ($P = 0.008$). The usage of combined therapy significantly increased the absorbing activity of monocytes as compared with the usage DC vaccine only. It was observed the increase of absorbing activity by 47% ($P = 0.048$) in the group CIT 2, that proves the efficiency of combination DC-therapy with the low doses of cisplatin. According to the obtained results we made a conclusion that CIT 2 is the most effective CIT, because of the increase of phagocyte activity of splenocytes.

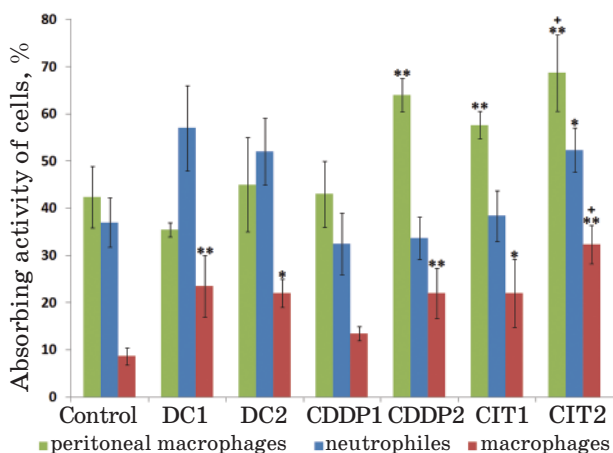


Fig. 4. Absorbing activity of phagocytes as a response for antitumor therapy of CBA mice:

here and for Fig. 5:

* — $P < 0.05$;

** — $P < 0.025$ as compared with the control group;

+ — $P < 0.05$ as compared with the DC2 group)

The ability of phagocytes to produce active oxygen forms (AOF) is the form of antitumor defence of the organism. The AOF production takes place during “oxygen explosion” in the middle of phagosomes and in the ambient that provides cytotoxic action on immunologically incompatible and tumor cells [15]. In general, the generation of AOF occurs in phagocytes during “oxygen explosion” with the aid of NADPH oxidase system [11]. We showed that significant increase of AOF production by peritoneal macrophages took place in case of CIT 2 (Fig. 5). Coefficient of stimulation of AOF production by peritoneal macrophages was increased by 73% as compared with the control ($P = 0.049$). Activating action of AOF on phagocytes in the CIT 2 group was much more than this one in DC2. It was established that coefficient of stimulation of AOF production by peritoneal macrophages was increased by 60% as compared with DC2 ($P = 0.028$).

CIT passage provides the increase of AOF generation by splenocytes which according to morphological characteristics are identical to macrophage and neutrophiles. It has to be noted that in CIT 2 group we observed the increase of coefficient of stimulation of AOF production by spleen cells, particularly neutrophils, by 68.6% ($P = 0.012$) and by macrophages — by 24.0% ($P = 0.049$) as compared with the control. In the other groups of animals the significant changes in coefficient of stimulation of AOF production by peritoneal macrophages and splenocytes were not observed.

So, we observed maximal antitumor and immunomodulating effects after DC vaccine injection in combination with low doses of cisplatin, 2 mg/kg (CIT 2). In case of CIT 1 we

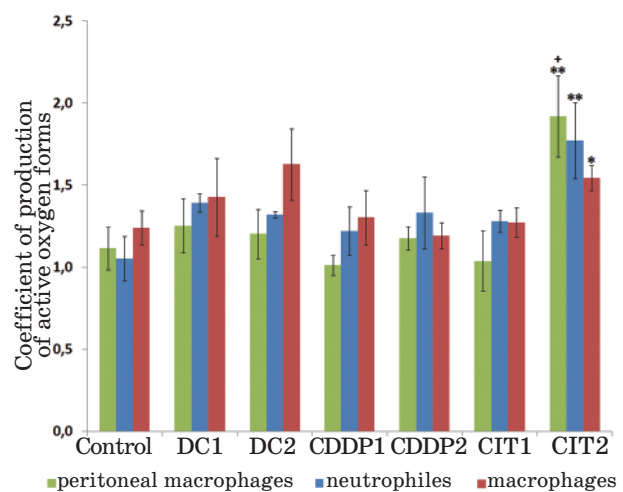


Fig. 5. Coefficient of production of active oxygen forms by splenocytes from CBA mice as a response for CIT

also observed the increase of antitumor immune response at the animals, but there was not any significant influence on tumor growth. Among the important immunomodulating effects of CIT2 we have to note the strengthening of functional activity of natural immunity, in particular the increase of cytotoxic activity of NKC, absorbing activity and ability to produce AOF by peritoneal macrophages, neutrophils and spleen macrophages.

It can be suggested that cisplatin in dose of 2 mg/kg promotes the elimination of suppressor cells of tumor microenvironment and system suppressor cells. This, in its turn, provides the increase of reaction ability of immune system as a response on DC vaccine. The results prove expediency of combining of therapeutic approach-

es in such cases, when the usage of DC vaccine and cytostatics leads to synergism of their actions.

So, we obtained the experimental proves of the promising usage of the proposed scheme CIT 2 for therapy of tumor. It can be stated the following:

1. Chemoimmunotherapy based on DC vaccine usage and cisplatin low doses possesses significant antitumor and immunomodulatory effects at the tumor-bearing animals.

2. The most efficient scheme is the combination of cisplatin in dose of 2 mg/kg and DC vaccine, when these approaches are consistently used.

3. The obtained data is the base for further investigation of above-mentioned scheme of combining chemoimmunotherapy for tumor treatment.

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ЗАСТОСУВАННЯ ХІМІОІМУНОТЕРАПІЇ НА ОСНОВІ ДЕНДРИТНИХ КЛІТИН ТА ЦИСПЛАТИНУ В ЕКСПЕРИМЕНТІ

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Метою роботи було опрацювати схему комбінованої хіміоімунотерапії, а також дослідити протипухлинну та імуномодулювальну активність хіміоімунотерапевтичного режиму із застосуванням вакцини на основі дендритних клітин і низьких доз цисплатину у мишей лінії СВА із саркомою-37. Максимальний протипухлинний та імуномодулювальний ефекти спостерігаються після застосування вакцини на основі дендритних клітин у комбінації з дозами цисплатину в концентрації 2 мг/кг. Серед значних імуномодулювальних ефектів комбінованої терапії слід відзначити посилення функціональної активності природної ланки імунітету, зокрема підвищення цитотоксичної активності природних кілерних клітин, поглинальної активності та здатності до продукування активних форм кисню перитонеальних макрофагів, нейтрофілів і макрофагів селезінки. Результати дослідження свідчать про доцільність комбінування хіміо- та імунотерапевтичних методів при розробленні більш ефективних підходів для профілактики рецидивів і метастазів у хворих на злоякісні новоутворення після основного лікування.

Ключові слова: саркома-37, вакцина на основі дендритних клітин, цисплатин, хіміоімунотерапія.

ПРИМЕНЕНИЕ ХИМИОИМУНОТЕРАПИИ НА ОСНОВЕ ДЕНДРИТНЫХ КЛЕТОК И ЦИСПЛАТИНА В ЭКСПЕРИМЕНТЕ

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Целью работы была разработка схемы комбинированной химиоиммунотерапии, а также исследование противоопухолевой и иммуномодулирующей активности химиоиммунотерапевтического режима с применением вакцины на основе дендритных клеток и низких доз цисплатина у мышей линии СВА с саркомой-37. Максимальный противоопухолевый и иммуномодулирующий эффекты наблюдаются после применения вакцины на основе дендритных клеток в комбинации с дозами цисплатина в концентрации 2 мг/кг. Среди значительных иммуномодулирующих эффектов комбинированной терапии следует отметить усиление функциональной активности естественного звена иммунитета, в частности повышение цитотоксической активности природных киллерных клеток, поглощающей активности и способности к продуцированию активных форм кислорода перитонеальных макрофагов, нейтрофилов и макрофагов селезенки. Результаты исследования свидетельствуют о целесообразности комбинирования химио- и иммунотерапевтических методов при разработке более эффективных подходов для профилактики рецидивов и метастазов после основного лечения у больных злокачественными новообразованиями.

Ключевые слова: саркома-37, вакцина на основе дендритных клеток, цисплатин, химиоиммунотерапия.