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ANTITUMOR EFFICACY OF LIPOSOMAL DOXORUBICIN HYDROCHLORIDE IN COMBINATION WITH TAMOXIFEN. EXPERIMENTAL STUDY

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ABSTRACT — In this paper we evaluated the effectiveness of adjuvant chemotherapy in animals (n=30), which created a model of cancerogenesis. We created 3 equal studies: the 1st group control (n=10) – animals were monitored without treatment; the 2nd group (n=10) — animals received adjuvant therapy with a combination of drugs: liposomal doxorubicin hydrochloride+tamoxifen;the 3rd group (n=10) — animals received adjuvant therapy in a combination of doxorubicin hydrochloride (non-liposomal)+tamoxifen. All animals were monitored for a total of 30 days. As a result, the volume of the tumor in the group of animals treated with liposomal doxorubicin hydrochloride was almost 3 times less than in the control group, and 2 times less than in the rats treated with simple doxorubicin. We also recorded a significantly lower number of lung metastases in animals of the second group compared to other groups. Conclusion. Treatment of Walker 256 tumors with liposomal doxorubicin showed better efficacy and safety compared to non-liposomal doxorubicin.

KEYWORDS — Liposomal doxorubicin hydrochloride, adjuvant chemotherapy, breast cancer, tumor of the Walker strain, metastasis.

INTRODUCTION

Breast cancer (BC) takes the 1st place in the structure of oncological diseases in women [1, 2, 3, 4]. The incidence of breast cancer has been steadily increasing by 1–2% every year [3]. Every year, oncologists all over the world register more than 1 million new cases of breast cancer [1, 5]. Over the last ten years, there has been an increase in the incidence of breast cancer in Russia by 29.1% [5]. Adjuvant chemotherapy is actively used in the treatment of BC [2]. Doctors use adjuvant chemotherapy to achieve several goals: reducing the volume of the primary tumor; reducing the size and number of affected lymph nodes; increase in the number of conservative surgical interventions; elimination of distant micrometastases, etc. [3, 6, 7].

According to modern rules of adjuvant chemotherapy, it is recommended to use a combination of chemotherapy drugs to potentiate the antitumor effect and reduce toxic effects. Thus, a combination of cytostatic and antiestrogenic drugs is most often used in adjuvant chemotherapy of BC.

Aim:

To evaluate the effectiveness of combined adjuvant chemotherapy using liposomal doxorubicin hydrochloride in combination with tamoxifen.

METHODS

This was an experimental study that we conducted on 30 non-linear white rats weighing 200–250 g, which were kept in the vivarium of the National Research Ogarev Mordovia State University (Republic of Mordovia, Russian Federation). All manipulations with animals were carried out in accordance with the Guidelines for the maintenance and use of laboratory animals. All interventions that cause pain in animals were performed under anaesthesia.

At first, we created a model of a tumor in animals by injecting 1.2 ml of suspension into the hind right paw, which contains 2 tumor strains (solid Walker 256 tumor strain and solid transferable tumor strain). We examined all the animals daily and registered the appearance of tumors. Every three days we examined all the rats. The tumor model was formed on the 5th day, after which all the rats were divided into three groups:

The 1st group: the control group rats (n=10) that were observed and didn't receive any therapy,

The 2nd group: the rats (n=10) which received neoadjuvant therapy with a combination of drugs: tamoxifen + liposomal doxorubicin hydrochloride (5mg/kg/ml) intravenously one time on the 5th day after tumor transplantation.

The 3rd group: the rats (n=10) which received neoadjuvant therapy with a combination of drugs:

tamoxifen + doxorubicin hydrochloride (non-liposomal) at a dose of 5 mg/kg/ml intravenously one time on the 5th day after tumor transplantation.

In animals of the 2nd and 3rd groups, we used tamoxifen in the neoadjuvant mode. The drug was administered daily, in the abdominal cavity, at a dose of 0.5 mg/kg from 5th to 30th days of the experiment. We evaluated the effectiveness of antitumor therapy by measuring the size of tumors and the dynamics of their regression. We also calculated the number of lung metastases after the experiment was completed. The reliability of differences between quantitative indicators was assessed using the Mann–Whitney test. The differences were considered significant at $p < 0.05$.

RESULTS

Our observation showed stable tumor growth in a control group of animals (Fig. 1). We recorded a significant inhibition of tumor node growth in the second group of rats on the 18th day from the beginning of the experiment compared to the first and third groups: 36604.90, 71652.26 and 69781.11 mm^3, respectively ($p<0.05$). We also noted by the end of 3 weeks of the experiment the formation of a tumor regression tendency in the 2nd and 3rd groups of animals, which was reliably maintained until the end of observation (Fig. 1). In the 2nd group. where rats were treated with liposomal doxorubicin hydrochloride in combination with an antiestogenic drug, the volume of tumors was the smallest at the end of the experiment (Fig. 1). Consequently, the liposomal doxorubicin has the ability to suppress tumor growth.

We recorded a significant difference in the number of lung metastases between groups ($p<0.05$) (Fig. 2).

The absence of lethal outcomes among animals of the second group is an indicator of the advantage of combined adjuvant therapy with liposomal doxorubicin hydrochloride. In the control group of rats, there were 20% fatalities, and in the third group (treatment with non-liposomal doxorubicin hydrochloride) — 40% ($p<0.05$).

DISCUSSION

Doxorubicin-based chemotherapy is one of the most effective antitumor agents for various stages of breast cancer [8]. However, the clear cytostatic benefits of doxorubicin hydrochloride were limited by the drug's toxicity, especially the risk of heart and liver complications. Previously, researchers tried to reduce the toxicity of doxorubicin by changing its dosage [2]. Currently, it is possible to use modified liposomal doxorubicin hydrochloride to improve the antitumor effectiveness of the drug and reduce its cardiotoxicity [9]. Liposomal doxorubicin hydrochloride contains

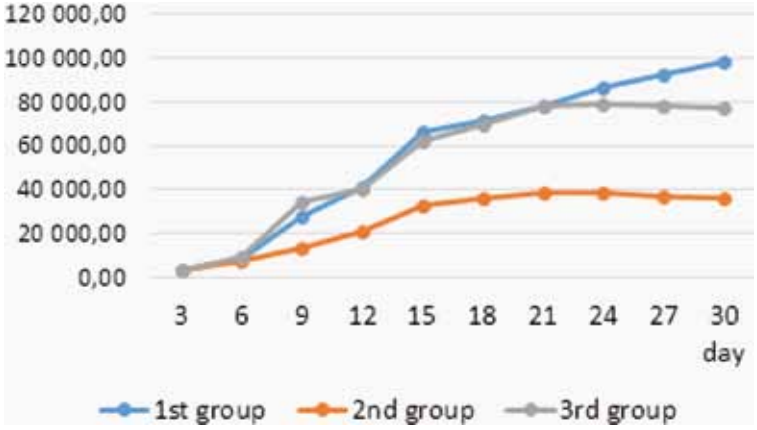

Fig. 1. Dynamics of tumor growth (mm^3) depending on the type and duration of adjuvant combination therapy

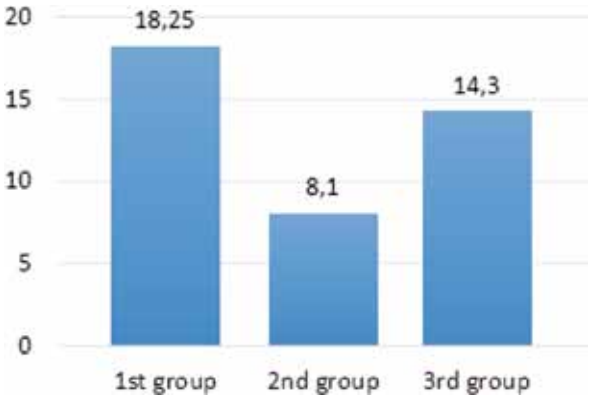

Fig. 2. The number of lung metastases in rats on 30th days of the study

hydrophilic polymers of methoxypolyethylene glycol (liposomes) in contrast to non-liposomal doxorubicin hydrochloride. This creates an advantage for the first drug, since the protection of the molecule from the reaction of the host phagocytic system is formed, which allows extending the time of circulation of the cytostatic substance in the bloodstream and ensuring its higher concentration in the tumor tissue [3]. Fukuda A. et al. claim that liposomal doxorubicin hydrochloride causes less pronounced myelosuppression, cardiotoxicity, and alopecia compared to non-liposomal doxorubicin [9]. Later, Franco YL et al. confirmed that liposomal doxorubicin hydrochloride has low cardiotoxicity, which makes it possible to use this drug in elderly patients [8]. Our study showed that in the group of animals treated with liposomal doxorubicin hydrochloride, the volume of the tumor was almost 3 times less than in the control group, and 2 times less than in the rats treated with simple doxo-

rubicin. We also recorded a significantly lower number of lung metastases in animals of the second group by almost 2.5 and 2 times compared to the first and third groups, respectively. According to Lu YC et al. the use of liposomal doxorubicin hydrochloride may extend the period of relapse-free survival in patients with stage I–III breast cancer [10].

CONCLUSIONS

The most effective combination of antitumor drugs in the treatment of Walker 256 tumors in white rats is a scheme that includes liposomal doxorubicin in combination with tamoxifen in a therapeutic mode. Liposomal doxorubicin provides high safety and effectiveness in tumor growth inhibiting.

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