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ANTIOXIDANT EFFECTS OF EMOXYPINE AS ADJUVANT OF ANTI-CANCER DRUGS

АНТИОКСИДАНТНЫЕ ЭФФЕКТЫ ЭМОКСИПИНА В КАЧЕСТВЕ АДЪЮВАНТА ПРОТИВООПУХОЛЕВЫХ ПРЕПАРАТОВ

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Антиоксиданты, как известно, минимизируют окислительный стресс, взаимодействуя со свободными радикалами, образующимися в результате клеточных аэробных реакций. Окислительный стресс связан со многими заболеваниями, особенно с опухолями. Поэтому антиоксиданты играют решающую роль в профилактике или лечении заболеваний, связанных с функционированием свободных радикалов. Однако большинство антиоксидантов оказывают противоопухолевое действие только при приеме в больших дозах. Поэтому комбинированное применение антиоксидантов с химиотерапевтическими средствами является привлекательной стратегией борьбы с различными опухолями. Эта статья посвящена антиоксидантным свойствам эмоксипина. Показан вклад данного соединения в усиление противоопухолевых свойств неларабина.

Antioxidants are known to minimize oxidative stress by interacting with free radicals produced as a result of cell aerobic reactions. Oxidative stress has long been linked to many diseases, especially tumours. Therefore, antioxidants play a crucial role in the prevention or management of free radical-related diseases. However, most of these antioxidants have anticancer effects only if taken in large doses. Therefore, the combined use of antioxidants with chemotherapeutic agents is an attractive strategy to combat various tumours. This article focuses on the antioxidant effect of emoxypine. The contribution of this molecule in enhancing the anticancer potentials of nelarabine will be demonstrated.

Ключевые слова: модифицированные нуклеозиды, антиоксиданты, активные формы кислорода, рак, неларабин, эмоксипин.

Keywords: modified nucleotides, antioxidants, reactive oxygen species, cancer, nelarabine, emoxypine.

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Reactive oxygen species (ROS) are normal products of the aerobic metabolic reaction of the cell. They contain oxygen in the form of peroxides and superoxide hydroxyl radicals, singlet oxygen or hydrogen peroxide. ROS can be produced in increased amounts under pathophysiological conditions. ROS is usually induced endogenously by enzymes that generate ROS, such as xanthine oxidase, and metabolic byproducts generated in an electron transfer chain reaction. Externally, many factors, including environmental stress such as exposure to ionizing radiation or excessive ultraviolet (UV) radiation, can increase ROS production. ROS can damage cell membranes, lipids, proteins and DNA, causing serious damage and disruption of their normal functions. This can lead to mutations, apoptosis and failures in these systems [1]. Oxidative stress, an imbalance between ROS production and antioxidant defense mechanisms, thus occurs due to the inability of endogenous antioxidant defense mechanisms to protect against these disorders. This can lead to the development and exacerbation of many painful conditions, such as diabetes, Parkinson's disease, Alzheimer's disease,

acute renal failure, pulmonary failure, and cancer [2]. Therefore, taking antioxidant supplements is recommended to reduce oxidative damage to the human body. Antioxidants usually exert their effect primarily by either preventing ROS production or by absorbing the ROS produced. Some types of antioxidants are active by breaking down ROS into less harmful or neutral foods. When treating cancer, chemotherapy causes an increase in the production of reactive oxygen species (ROS) in cancer cells. Antioxidants have a great impact on cancer treatment and protection.

The effects of ROS can be two-sided: they can kill both normal and cancer cells by damaging proteins, lipids and DNA, or even cause cancer. In contrast, manipulations with ROS can induce apoptosis in cancer cells only because normal cells have a different redox environment than cancer cells and are less sensitive to redox manipulations. Therefore, modulation of ROS by antioxidants or prooxidants is a promising strategy for selectively targeting cancer cells during chemotherapy treatment [3].

Numerous original research articles have focused on whether additional antioxidants given during chemotherapy can protect normal tissues without adversely affecting tumor damage. Due to differences in study design, protocol of intervention, type of cancer, follow-up time, inclusive criteria, statistical analysis and chemotherapy regimen, uncertainties arise that allow a definitive conclusion regarding the risk of reduced tumor control due to the introduction of additional antioxidants during chemotherapy. Previous in vitro studies have shown that cytarabine and other related cytosine-based nucleoside analogs are toxic to tumor cells by increasing the level of cellular oxidative stress, since it can be neutralized by antioxidants [4]. In contrast, a recent review unequivocally concluded that the antioxidant, when used simultaneously, (a) does not interfere with chemotherapy, (b) enhances the cytotoxic effect of chemotherapy, (c) protects normal tissues, and (d) increases patient survival and therapeutic response. [5].

However, very little is known about the effect of combinations of antimetabolites with antioxidants on cytotoxic innate and adaptive immune cells, and whether the toxicity of lymphocytes affects its anticancer efficacy.

Therefore, in the present study, we investigated the effect of various concentrations of nelarabine (an anticancer drug) in vitro with emoxypine (as an antioxidant) or without it on the HepG2 liver cancer cell line.

Nelarabine is an analogue of a purine nucleoside (Fig. 1), converted into the corresponding arabinosyl guanine nucleoside triphosphate (araGTP), which leads to inhibition of DNA synthesis and cytotoxicity.

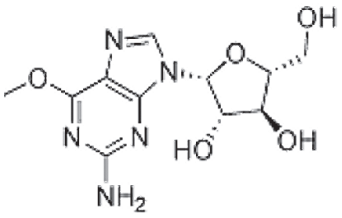

Fig. 1 – Structural formula of nelarabine

Purine nucleoside analogs enter cells through specific nucleoside carriers: concentrating and balancing nucleoside carriers. Carriers of organic ions, as well as carriers of peptides, can also participate in the uptake of certain analogs by cells and viruses.

Once inside the cell, the nucleoside analog undergoes an initial stage of rate-limiting phosphorylation by side kinase, which leads to the production of a monophosphate metabolite. Then the second stage of phosphorylation is performed by nucleoside monophosphate kinase, and the third stage of phosphorylation is performed by nucleoside diphosphate kinase. Triphosphates can be incorporated into nucleic acids by competing with endogenous nucleoside triphosphates, or they can inhibit DNA and RNA synthesis by inhibiting basic enzymes such as polymerases. In addition, ribonucleotide reductase M1 (RRM1), a key enzyme involved in nucleotide metabolism, can be inhibited by both diphosphorylated and triphosphorylated analogs. Catabolic enzymes can reduce the amount of active metabolites, including deaminases and 5'-nucleotidases.

Nelarabine itself is used to treat T-cell acute lymphoblastic leukemia (ALL) and T-cell lymphoblastic lymphoma by slowing or stopping cell growth.

Emoxipine is a 3-hydroxypyridine derivative (Fig. 2) with powerful antioxidant properties. In medicine emoxypine is used as a drug from the group of antiplatelet agents and antioxidants, it is a microcirculation corrector. The active component of the drug, methyl ethyl pyridine, after penetration into the bloodstream, strengthens the vessels, prevents them from rupture, and thins the blood, thereby preventing the development of destructive processes in the lumen of the nipples.

The antioxidant effect of the drug "Emoxypine" allows you to stimulate natural processes, to neutralize free radicals, thereby preventing damage to vital biological molecules.

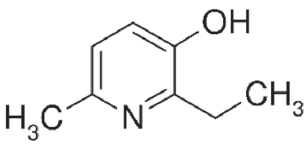

Fig. 2 – Structural formula of emoxypine

The form:

$$\varphi(\mathrm{x}) = c + \frac{d-c}{1+e^{b\,(\log x - \log e)}}\ .$$

The estimated parameters of the models have a definite physical meaning. In particular, for the log-logistic model, the parameters *c* and *d* determine the lower and upper horizontal asymptotes of the sigmoid curve, *e* corresponds to the position of the inflection point, and *b* – to the angle of inclination in the transition region. Fitting of model parameters to the analyzed empirical data was carried out using the generalized method of minimizing the sum of squares of deviations of model forecasts from the observed values, taking into account specially selected weight coefficients.

Statistical analysis of the estimated parameters was carried out using Student's t-test, which tested the hypothesis of the equality of each coefficient to zero and calculated *p*-values that determine the achieved level of significance. The statistical significance of the model as a whole was verified by comparing it with a simple regression with a zero slope coefficient (the horizontal regression line corresponds to the absence of dose-effect dependence) by ANOVA.

The results of experimental data are provided at the fig. 3.

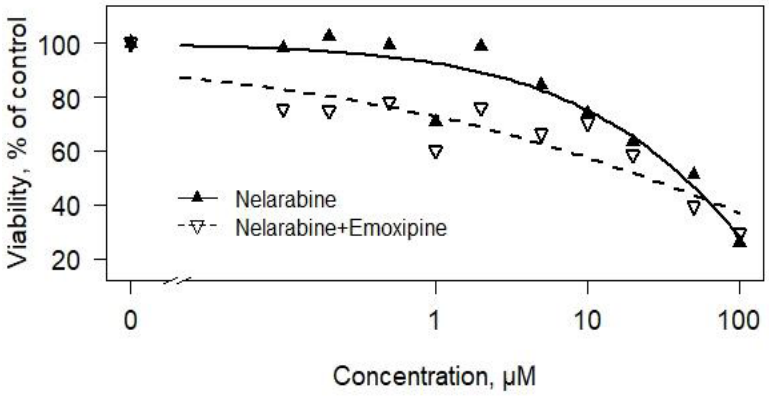

Fig. 3 – Viability of liver cancer cell line HepG2 after exposure to nelarabine or combination of nelarabine with emoxypine

As can be seen from the data presented at fig. 3, both nelarabine and the combination of nelarabine and emoxypine in the studied concentration range (10^{-4} to 10^{-7} M) lead to 70% reduction in cell viability compared to control.

Statistical analysis of the significance of the estimated model parameters for the studied compounds according to the *t*-criterion leads to the following values of *p*-values (table 1).

Table 1 – Parameter estimates of model of impact of nelarabine or combination of nelarabine with emoxypine on liver cancer cell line HepG2

Параметр	Estimate (μM)	Std. Error	*t*-value	*p*-value
b: Slope (nelarabine)	0.68	0.15	4.5435	$2.562*10^{-05}$ ***
b: Slope (nelarabine with emoxypine)	0.26	0.049	5.3079	$1.531*10^{-06}$ ***
c: lower limit	24.19	38.05	-1.1613	0.2499
d: upper limit	98.45	3.14	31.3226	$< 2.2*10^{-16}$ ***
e: ED_{50} (nelarabine)	111.25	84.65	1.3143	0.1935
e: ED_{50} (nelarabine with emoxypine)	307.83	516.93	0.5955	0.5536

*Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1*

As can be seen from the data presented in the table, slope (*b*) and upper limit (*c*) quotients are statistically significant for nelarabine and combination of nelarabine and emoxypine, while they were not statistically significant for the rest of the model parameters.

The log-logistic model «dose-effect» for nelarabine looks like:

$$\varphi(\%\ of\ control) = 24{,}19 + \frac{98{,}45 - 24{,}19}{1 + e^{0{,}68*(\log C(\mu M) - \log 111{,}25)}}.$$

The log-logistic model «dose-effect» for the combination of nelarabine and emoxypine looks like:

$$\varphi(\%\ of\ control) = 24{,}19 + \frac{98{,}45 - 24{,}19}{1 + e^{0{,}26*(\log C(\mu M) - \log 307{,}83)}}.$$

Analysis of variances (ANOVA) showed no statistically significant differences between the effects of nelarabine and combination of nelarabine and emoxypine ($F = 0.5091$, $p = 0.6036$).

Our results show that antioxidant emoxypine not only does not affect the main function of antimetabolite nelarabine, namely: to interrupt the cell division and growth, but also looks like it modulates its action. Our results contribute to a better

understanding of the molecular mechanisms of the effect of nucleic acids antimetabolites on biochemical processes, which can serve as the basis for the targeted search and creation of new anticancer drugs.

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МикроРНК let-7e И miR-140 КАК БИОМАРКЕРЫ ДЕФОРМИРУЮЩИХ ЗАБОЛЕВАНИЙ СУСТАВОВ

MicroRNA let-7e AND miR-140 AS BIOMARKERS OF DEFORMING JOINT DISEASES

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Исследован уровень экспрессии циркулирующих микроРНК let-7e и miR-140 в плазме периферической крови и синовиальной жидкости пациентов с гонартрозом и коксартрозом. Выявлено статистически значимое снижение экспрессии miR-140 в синовиальной жидкости и let-7e в периферической крови пациентов с остеоартритами ($p<0,05$). МикроРНК let-7e характеризует сопутствующую патологию и указывает на развитие метаболического синдрома. Установлена корреляционная связь уровней экспрессии изучаемых микроРНК со степенью тяжести заболевания.

The circulating microRNAs (let-7e and miR-140) expression levels were studied in the plasma of peripheral blood and synovial fluid of patients with gonarthrosis and coxarthrosis. There was a statistically significant decrease in the expression of miR-140 in synovial fluid and let-7e in the peripheral blood of patients with osteoarthritis ($p <0.05$). MicroRNA let-7e characterizes comorbidity and indicates the development of metabolic syndrome. It was established a correlation between the microRNAs expression levels and the disease severity.

Ключевые слова: микроРНК, синовиальная жидкость, периферическая кровь, остеоартрит, тяжесть течения, биомаркер.

Keywords: microRNA, synovial fluid, peripheral blood, osteoarthritis, severity, biomarker.

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Остеоартрит – дегенеративно-дистрофическое заболевание суставов, распространенность которого увеличивается, занимая первое место среди всех нозологических форм патологии суставов и поражая не менее 20% населения. В Республике Беларусь отмечается неуклонный рост заболеваемости остеоартритами, при этом все чаще поражая молодое население. Актуальность изучения данной патологии также обусловлена высоким уровнем временной нетрудоспособности, ранней инвалидизацией населения и ухудшением качества жизни пациентов в целом.

В настоящее время описаны клинические фенотипы пациентов с остеоартритами, однако патогенетические механизмы развития и достоверные методы лабораторной диагностики, в том числе молекулярно-генетические, гонартрозов и коксартрозов до конца не изучены, что затрудняет постановку диагноза, а также прогнозирование исход.

В качестве биологических маркеров остеоартритов могут быть использованы малые некодирующие РНК, в частности, микроРНК. В связи с небольшим количеством нуклеотидов, формирующих уникальную последовательность микроРНК, данный вид нуклеиновой кислоты характеризуется крайне низкой изменчивостью, и, соответственно, высоким постоянством: микроРНК имеют мало шансов на вариацию или мутацию. Однако известно, что воздействия лекарственных препаратов, различных внешних стимулов, влияющих на генетические и эпиге-