Landomycin A is a new antibiotic of angucycline group with antineoplastic activity against tumor cells of different origin. In this work, we investigated the effects of landomycin A on the growth of B16F10 mouse melanoma. It was elucidated that studied antibiotic possessed a significant dose-dependent cytotoxic activity against these melanoma cells in vitro, and its LC50 = 2 µM was 5 times lower than that of the doxorubicin, anticancer drug widely used for treatment of solid tumors. Landomycin A at concentration of 10 mg/kg body weight did not cause pathological changes, mortality or general toxic symptoms in intact mice of C57black/6 line. No significant changes in the body weight and hematological parameters of animals treated with landomycin A as compared to the control group were observed. While B16F10 melanoma maintained rapid growth in vivo with a continual increase in tumor volume, landomycin A effectively inhibited tumor growth without a marked myelosuppressive effects or cardio- and hepatotoxicity that are characteristic for doxorubicin action. These results suggest a perspective of landomycin A application in chemotherapy of malignant tumors.

**Keywords**: landomycin A, melanoma, tumor volume, oxidative therapy.

**INTRODUCTION**

A cutaneous melanoma is a highly malignant tumor derived from melanocytes, the pigment-producing cells in skin epidermis [14]. If being early diagnosed and surgically removed while localized in the outermost skin layer, melanoma is potentially curable. When tumor cells have spread to distant lymph nodes or metastasized (stage IV), they become refractory to common chemotherapies and, therefore, incurable. The prognosis for patients with stage IV metastatic melanoma is very poor, with an expected median survival of only 6 to 9 months [7]. The rapid increase in the incidence of malignant melanomas has not been associated with any improved therapeutic options over the years [2].
Landomycin A (LA) is a new angucycline antibiotic with potential antitumor action. It consists of benzoanthracene tetracyclic aglycone and hexasaccharide chain that comprise two repetitive trisaccharide subunits (α-L-rhodinose-(1-3)-β-D-olivose-(1-4)-β-D-olivose) joined by O-glycoside bond (Fig. 1).

LA exhibits a strong cytotoxic effect towards tumor cells of different origin and induces early apoptosis in target cells. Our finding that landomycin A induces oxidative stress in cancer cell lines in vitro provides a possible mechanism of its antineoplastic activity [8]. It is known that cancer cells have increased ROS steady state level, and they are likely to be more vulnerable to damage by further ROS insults induced by exogenous agents [4]. Thus, manipulating ROS levels by redox modulation could be a way to kill cancer cells selectively without causing a significant toxicity to normal cells. Melanoma is a unique type of cancer with melanin biosynthesis that produces high level of ROS and oxidative stress [10, 15]. Thus, melanoma cells are expected to be very sensitive to therapeutic strategies whose application leads to induce cancer cell death through ROS production.

In this study, we evaluated the effects of landomycin A in vitro and in vivo on the growth of mouse melanoma cells.

MATERIALS AND METHODS

Landomycin A (99% purity according to thin-layer chromatography) was obtained in the laboratory of professor Jurgen Rohr (Department of Pharmaceutical Sciences, University of Kentucky, USA). Doxorubicin hydrochloride (Dx, Pfizer, New York, NY) was bought in local pharmacy.

Cell culture. B16F10 cell line (mouse melanoma) used in this study was obtained from the collection of the Institute of Cancer Research at Medical University of Vienna (Austria). Cells were grown in RPMI-1640 medium (Sigma, USA) supplemented with 10% fetal bovine serum (Sigma, USA) and 50 µg/ml gentamicin (Sigma, Missouri, USA) in 5% CO₂-containing humidified atmosphere at 37 °C. Cells were re-seeded every two days at the rate of 2.5×10⁵ cell/ml of culture medium [1].

Cytotoxicity assay. Cytotoxicity was measured using Trypan Blue exclusion assay. Briefly, exponentially growing B16F10 cells at 1×10⁵ cells/well density were treated
with various concentrations of studied drug and cultivated in a 24-well tissue culture plate (Greiner Bio One, Frickenhausen, Germany). After 24 h incubation, the number of cells was calculated in the hemocytometer chamber by counting the number of dead cells using 0.1% Trypan Blue dye that stains dead cells with damaged membrane in blue, whereas alive cells remain unstained [5].

**Animals.** Studies of the biological activity of LA were conducted using male C57black/6 mice Kent at animal facility of the Institute of Cell Biology, NAS of Ukraine (Lviv, Ukraine). All in vivo experiments were conducted in accordance with the international principles of the European Convention for protection of vertebrate animals under a control of the Bio-Ethics Committee of the above mentioned institution (Protocol N 9/2015 from 1.09.2015 of the BioEthics committee of the Institute of Cell Biology, NAS of Ukraine). Animals weighing 18–25 g were kept at a temperature of 22±2 °C and with photo cycle of 12-hour light/12-hour dark. Water and food pellets were provided *ad libitum*.

**Testing of LA in vivo toxicity.** To define the toxicity of studied compound three experimental groups of male C57black/6 mice were used. Animals were distributed according to the study design: 1<sup>st</sup> group – control, intact animals, 2<sup>nd</sup> group – animals treated intraperitonealy (IP) with LA (10 mg/kg), 3<sup>rd</sup> group – mice treated IP with Dx (cumulative dose 10 mg/kg). There were three mice used in each group. During the period of study, the animals were weighed every day. Clinical symptoms were evaluated in mice daily.

**Blood cell formula.** For blood sampling amputation of small part of mouse tail was cut with pumping of ~100 µl of blood in a test tube, followed by immediate disinfection of a wound with 70% alcohol. For counting of red blood cells, 5 µl of blood were dissolved in 5 ml of isotonic NaCl solution (1:1000 dilution), while for leukocyte, 5 µl of blood were dissolved in 95 µl of 3% acetic acid solution (1:20 dilution). Erythrocytes and leukocytes were counted under the Evolution 300 Trino microscope (Delta Optical, Mińsk Mazowiecki, Poland) and calculated by standard formulas, described in [11]. For blood smear preparation, 3 µl of blood were put at the edge of a slide, and then spread for 1.5 cm using another narrow polished slide, placed at a 45° angle. The obtained smears were dried at room temperature, then fixed with absolute methanol, and later rehydrated by subsequent washing in ethanol solutions with decreasing concentration (96%, 75%, 50%, 25%, 12.5%). Finally, the smears were washed with distilled water, stained with Giemsa dye and air-dried, after which they were ready for analysis of leukogram. Counting of leukocytes was performed under Evolution 300 Trino microscope (Delta Optical, Mińsk Mazowiecki, Poland) using 90× oil immersion objective. Cell counting was always done using the same system – half of cells were counted in the upper half part of the smear, and the rest 50% of cells were counted on the lower part of the smear. A percentage of certain types of white blood cells in each smear was determined after counting of at least 300 cells.

**Tumor implantation.** Tumor inoculation was done by a subcutaneous injection of B16F10 cells suspension diluted with sterile 1-x phosphate-buffered saline (PBS) in an amount of 1 mln per one animal. The viability and number of cells stained with 0.1% Trypan Blue were checked by cell counting in the haemocytometric chamber. The vitality of melanoma cells used for transplantation was not less than 98%.

Animals were distributed according to study design: 1<sup>st</sup> group (n = 5) – intact animals, 2<sup>nd</sup> group (n = 5) – control animals with B16F10 melanoma, 3<sup>rd</sup> group (n = 5) – animals treated IP with LA (cumulative dose 10 mg/kg), 4<sup>th</sup> group (n = 3) – mice treated IP with Dx (cumulative dose 10 mg/kg).
LA and Dx were administered 5 times in dose of 2 mg/kg every 72 hours. Injections of studied compounds were performed on 10th day after tumor inoculation. The length, width, and height of tumors were measured every three days with calipers. Experiments were terminated on 22nd day, when tumor volumes in the control group reached the clinical endpoint (2500 mm³ or become necrotic) in accordance with animal ethics guidelines. Tumor volume was calculated as: \( \text{Vol} = \frac{1}{2} \text{L}_{\text{width}} \times \text{L}_{\text{length}} \times \text{L}_{\text{height}} \) [12].

**Aspartate and alanine aminotransferase activities.** For determination of aspartate aminotransferase activity (AST), 10 µl of blood serum were mixed with 100 µl of substrate solution (2 mM \( \alpha \)-ketoglutaric acid; 0.2 M D,L-aspartate in 0.1 M phosphate buffer pH 7.4), while in control tube 10 µl of distilled water were added instead of blood serum. The tubes were placed for 60 min at 37 °C, and then 100 µl of 1 mM solution of 2,4-dinitrophenylhydrazine was added to the samples and left for 20 min at RT. Then 1 ml of 0.4 M sodium hydroxide solution was added to each sample for extra 10 min, and optical density of samples was measured using ThermoSpectronic spectrophotometer (Helios, Great Britain) at 540 nm wavelength. For measuring alanine aminotransferase (ALT) activity, the procedure was identical except substrate solution (2 mM \( \alpha \)-ketoglutaric acid; 0.2 M D,L-alanine in phosphate buffer pH 7.4).

**Statistical analysis.** *In vitro* experiments were performed in triplicate for each variant. For statistical analysis, standard variation data within a group were calculated together with a statistical reliability of differences between two groups of data assessed by t-test. The level of significance was set at 0.05.

**RESULTS**

To determine the effect of LA on growth of B16F10 mouse melanoma *in vitro*, tumor cells were treated with studied drug at various concentrations (1, 2, 4, 6 µM) and examined by cell counting using Trypan Blue assay on 24 hour after LA addition to the culture medium. Compared with control group, cell density in groups treated with LA decreased significantly. Thus, LA effectively inhibits the growth of B16F10 cells (Fig. 2, A). It was shown that LA suppressed proliferation of melanoma cells in a dose-dependent manner. LC\(_{50}\) value (the concentration of compound which cause a death of 50% cells compared to the control) was 2 µM, which is about 5 times lower than for doxorubicin (IC\(_{50}\) for Dx on B16F10 cells = 10 µM, Fig. 2, B). Doxorubicin is considered to be gold chemotherapy standard and it is widely used for treatment of solid tumors [16].

![Fig. 2. Cytotoxic effect of landomycin A (LA, A) and doxorubicin (Dx, B) on B16F10 mouse melanoma cell line, 24 hours treatment](image-url)
The next step in our work was studying LA toxicity in male C57black/6 mice. This experiment was designed to investigate potential side effects of one-time IP administration of studied antibiotic in a dose of 10 mg/kg body weight. Fig. 3 demonstrates the results of weighing mice of control group.

![Graph](image1)

**Fig. 3.** Dynamics of C57black/6 mice body weight (control group) during the experiment. ▼ – day of blood collection, n = 3

It was shown that their body weight did not change during the experiment term. We did not reveal any pathological changes in the LA-treated mice, as compared to the control group of animals. No mortality or significant changes were observed in the body weight of mice that received LA (Fig. 4). A similar experiment, as above, was done with Dx. It was revealed (Fig. 5) that already after the first injection of Dx, the weight of experimental animals decreased by 8% in comparison to control group. Starting from the 9th day after the injection of last Dx dose the further decrease of weight of experimental animals took place. Mice of this group in 3 days lost about 16% of their body weight. Although the weight of animals did not return to the initial value, suggesting general toxic effect of this drug.

![Graph](image2)

**Fig. 4.** Dynamics of C57black/6 mice body weight during the experiment. ▼ – day of blood collection, ▼ – drug administration, n = 3

**Fig. 5.** Dynamics of C57black/6 mice body weight during the experiment. ▼ – day of blood collection, ▼ – day of drug administration, ▼ – final injection day, n = 3
The hematological profile (number of red and white blood cells as well as a leukogram) in the experimental animals was also studied. After LA administration, no significant changes in the peripheral blood cells were observed in comparing to animals of control group (Table 1).

**Table 1. Number of white, red blood cells and peripheral blood leukogram of mice on 7th day after the last injection of landomycin A and Doxorubicin**

| Blood cells                                      | Control     | Landomycin A | Doxorubicin |
|-------------------------------------------------|-------------|--------------|-------------|
| White blood cells (×10^3/μl)                     | 14.9±2.8    | 15.9±2.1     | 10.6±1.9*   |
| Red blood cells (×10^6/μl)                       | 9.5±0.7     | 9.1±0.6      | 8.7±0.6*    |
| Neutrophils with ring-shaped nuclei, RSN (%)     | 1.6±0.4     | 1.9±1.6      | 4.2±0.6     |
| Neutrophils with segmented nuclei, SN (%)       | 22.0±1.4    | 24.6±4.5     | 31.0±1.2    |
| Small lymphocytes, SL (%)                        | 72.0±1.4    | 70.3±4.7     | 58.6±0.9    |
| Big lymphocytes, BL (%)                          | 2.2±0.8     | 1.9±0.4      | 2.5±0.4     |
| Monocytes, M (%)                                 | 1.3±1.0     | 1.3±1.5      | 3.4±0.7*    |

**Comments:** * – statistically significant changes p<0.05 related to control

The relative increase in weight (%)

**Fig. 5.** Dynamics of C57black/6 mice body weight during the experiment. – day of blood collection, – drug administration, n = 3

**Рис. 5.** Динаміка маси тіла мишей C57black/6 протягом експерименту. – день забору крові, – день введення речовини, n = 3
(29% decrease in the amount of white blood cells compared to control group), erythrope-
nia (10% reduction in red blood cells number), diminution of SL percentage (from
72.0±1.4% in untreated mice to 58.6±0.9%) and increase in monocytes amount (from
1.3±1.0% to 3.4±0.7% were found (Table 1). These results prove low toxic nature of LA,
which is a primary criterion and important step in development of anticancer drugs.

B16F10 cells formed large, aggressive tumors in C57black/6 mice. To determine
whether LA limits melanoma growth in vivo, the IP injection of LA (cumulative dose
10 mg/kg) was carried out in B16F10 melanoma-bearing mice. As a result (Fig 6), the
mean of tumor volume was significantly less (742 mm$^3$) compared with that in control
group (3,126 mm$^3$) on 22$^{th}$ day when control mice were sacrificed. We also used Dx as
a positive control in the same dose (cumulative dose 10 mg/kg). Group of mice treated
with Dx also did show a decrease in tumor volume (1,878 mm$^3$ comparing with 3,126 mm$^3$
in control), however the tumor size in Dx-treated mice was 153% larger compared to LA
in the same concentration.

The hematological profile was also analyzed in B16F10 melanoma-bearing ani-
mals. The growth of B16F10 melanoma was characterized by a significant increase in
the level of SN (from 20.0±4.5% to 57.0±16.2%) and marked increase in the level of
WBC (from 6.2±0.9% to 13.5±1.7%). Regarding the leukogram in a group treated with
LA, it was revealed a restoration of these indicators found in control group, thus, sug-
gesting a therapeutic effect of this drug (Table 2).

The amount of SL is another important indicator that was decreased in tumor-bea-
rning animals (from 78.0±5.1% in intact mice to 31.9±4.1%). LA partially restored this
value to control level – from 31.9±4.1% to 54.0±10.6%.

Similar influence on above-mentioned indices was found at Dx action in the analo-
gous dose (Table 2). At the same time, we detected myelosuppression in the experi-
mental animals which is a negative side effect of this antibiotic that affecting proliferation

Fig. 6. Changes in tumor volume in B16F10 melanoma-bearing mice treated with Landomycin A (LA) and
Doxorubicin (Dx)

Рис. 6. Зміни об’єму пухлини у мишей із меланомою B16F10, що одержували ландоміцин A (ЛА) та до-
корубіцин (Дх)
of bone marrow cells, thus, leading to anemia. The amount of RBC decreased by almost
50% compared to intact control (from $10\pm0.9\times10^6/\mu l$ to $5.8\pm0.3\times10^6/\mu l$) and 20%
compared to mice with B16F10 melanoma ($7.3\pm0.3\times10^6/\mu l$ to $5.8\pm0.3\times10^6/\mu l$). A signifi-
cant increase (from $1.9\pm0.8\%$ in intact control to $9.5\pm2.6\%$) in a group treated with Dx
was observed in the number of monocytes.

**Table 2.** Number of white, red blood cells and peripheral blood leucogram of intact mice
and with B16F10 melanoma on 10th day after the last injection of landomycin A
and doxorubicin

| Blood cells | Control (intact animals) | Control B16F10 melanoma | Doxorubicin (cumulative dose 10 mg/kg) | Landomycin A (cumulative dose 10 mg/kg) |
|-------------|--------------------------|-------------------------|---------------------------------------|---------------------------------------|
| White blood cells ($\times10^3/\mu l$) | $6.2\pm0.9$ | $13.5\pm1.7^{#}$ | $8.2\pm2.4^{*}$ | $7.4\pm0.9^{*}$ |
| Red blood cells ($\times10^6/\mu l$) | $10.0\pm0.9$ | $7.3\pm1.4$ | $5.8\pm0.3^{***}$ | $7.2\pm0.5$ |
| Neutrophils with ring-shaped nuclei, RSN (%) | $0.5\pm0.2$ | $3.6\pm1.3$ | $2.9\pm1.8$ | $1.0\pm0.5$ |
| Neutrophils with segmented nuclei, SN (%) | $20.0\pm4.5$ | $57.2\pm1.2^{#}$ | $38.1\pm15.6$ | $38.4\pm9.3^{**}$ |
| Small lymphocytes, SL (%) | $78.0\pm5.1$ | $31.9\pm4.1^{#}$ | $42.7\pm16.8$ | $54.0\pm10.6^{*}$ |
| Big lymphocytes, BL (%) | $2.3\pm0.7$ | $5.7\pm4.7$ | $6.6\pm2.0$ | $3.0\pm2.0$ |
| Monocytes, M (%) | $1.9\pm0.8$ | $4.2\pm0.8$ | $9.5\pm2.6^{**}$ | $3.7\pm1.5$ |

**Comments:** * – statistically significant changes $p<0.05$ related to control (B16F10 melanoma); ** – $p<0.01$
related to control B16F10 melanoma; *** – $p<0.001$ related to control B16F10 melanoma; # – $p<0.05$
related to control (intact animals)

The activity of aspartate and alanine aminotransferases (AST and ALT) in blood
serum of LA, Dx treated mice was measured and AST/ALT correlation (De Ritis ratio)
were calculated for evaluating the effect of these drugs on liver and heart metabolism
(Table 3). It was shown that Dx increased in ALT/AST ratio (De Ritis ratio) from $1.3\pm0.1$
(normal value in healthy mice) to $1.8\pm0.1$ indicating hepato- and cardiotoxicity induced
under treatment [3]. This index also remained within normal limits ($1.2\pm0.2$) in animals
with B16F10 melanoma without treatment. In case of LA application, De Ritis ratio
increased insignificantly compared to control groups and showed $1.5\pm0.1$.

A therapeutic selectivity and avoiding resistance to drugs are two important issues
in the anticancer therapy. Strategies for improving therapeutic selectivity depend sig-
nificantly on understanding of the biological difference between tumor and normal cells.
Table 3. Impact of landomycin A and doxorubicin on ALT/AST levels in blood serum of B16F10 melanoma bearing mice on 10th day after last injection of drugs

Таблиця 3. Вплив ландоміцину А і доксорубіцину на рівень АСТ/АЛТ у сироватці тварин з меланою B16F10 на 10-й день після останньої ін’єкції речовин

| Variant of experiment                         | Aspartate aminotransferase (AST), units/ml×100 | Alanine aminotransferase (ALT), units/ml×100 | De Ritis ratio |
|---------------------------------------------|-----------------------------------------------|-------------------------------------------|----------------|
| Control (intact)                            | 1.68±0.00                                     | 1.33±0.00                                 | 1.3±0.1        |
| Control (B16F10 Melanoma)                   | 2.54±0.01                                     | 2.08±0.01                                 | 1.2±0.2        |
| Doxorubicin treatment                       | 1.83±0.01                                     | 1.03±0.00                                 | 1.8±0.1        |
| Landomycin A treatment                      | 1.83±0.01                                     | 1.22±0.01                                 | 1.5±0.1*       |

Comments: * – statistically significant changes p<0.05 related to intact control

Tumor cells, compared to normal ones are under big oxidative stress related to the oncogenic transformation and alterations in metabolic activity [13]. Exogenous agents that rapidly increase ROS generation will move the redox equilibrium and induce tumor cells death. In contrast, normal cells are less sensitive to agents that induce an oxidative stress due to low level of ROS production and high antioxidant capacity. Previously we have shown that under LA action in vitro, the level of ROS, mainly H$_2$O$_2$, had increased several times, comparing to control level already at the 1st hour after start of LA addition to the culture medium [8]. It is well established that high level of ROS, like H$_2$O$_2$, induce apoptosis in a wide variety of tumor cells via activating the caspase cascade [9]. We suppose that such early and rapid generation of ROS, accompanied with caspases activation allows LA to inhibit growth of B16F10 melanoma both in vitro and in vivo with much lower negative side effects than such effects of Dx.

CONCLUSION

In this study, we have shown that LA possessed antineoplastic effect towards B16F10 melanoma cells in vitro, and that effect was even stronger than such of Dx used as a positive control. LA’s action was not accompanied by cachexy in experimental animals and it didn’t cause hematotoxic effects found at Dx’s action. Our data on measurement of AST/ALT ratio testify to the lack of cardio- and hepatotoxicity under LA treatment. LA effectively inhibited growth of B16F10 melanoma in vivo without significant myelosuppressive effects.

Taking into consideration these results, investigation of action of LA in the other experimental tumor models that might be especially sensitive to this drug are desired, as well as studying the molecular mechanisms of its therapeutic activity.
ACKNOWLEDGEMENTS

We thank Prof. W. Berger from the Institute of Cancer Research at Medical University of Vienna for providing B16F10 melanoma cell line.

This work was partially supported by grants awarded to L. Lehka by West-Ukrainian BioMedical Research Centre (Ukraine-USA) in 2013–2014, and 2015–2016.

1. Adams R. Laboratory techniques in biochemistry and molecular biology. Elsevier, 1990. 16–94 p.
2. Atallah E., Flaherty L. Treatment of metastatic malignant melanoma. Curr. Treat. Options Oncol, 2005; 6(3): 185–193.
3. Botros M., Kenneth S. The De Ritis Ratio: The Test of Time. Clin. Biochem. Rev, 2013; 34: 117–130.
4. Chiara G., Isaac S., Harris M., Tak M. Modulation of oxidative stress as an anticancer strategy. Nat. Rev. Drug Discov, 2013; 12: 931–947.
5. Freshney R.I. Culture of animal cells: a manual of basic technique and specialized applications: Wiley-Backwell, 2010. 768 p.
6. Han S., Hong C., Kim H., Lyu S. Anti-cancer effects of enteric-coated polymers containing mistletoe lectin in murine melanoma cells in vitro and in vivo. Mol. Cell Biochem, 2015; 15: 1–15.
7. Korn E.L., Liu P.Y., Lee S.J. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J. Clin. Oncol, 2008; 26: 527–34.
8. Lehka L.V., Panchuk R.R., Berger W. et al. The role of reactive oxygen species in apoptosis of tumor cells induced by landomycin A. Ukrainian Biochemical Journal, 2015; 87(5): 72–82.
9. Matsura T., Kai M., Fujii Y., Yamada H. Hydrogen Peroxide-induced Apoptosis Requires Caspase-3 Activation in HL-60 Cells. Free Rad. Res, 1998; 30: 73–83.
10. Meyskens F.L., Jr. Farmer P., Fruehauf J.P. Redox regulation in human melanocytes and melanoma. Pigment Cell Res, 2001; 14: 148–54.
11. Ronin V.S., Utevsky N.L. Textbook for classes on the methods of clinical laboratory investigations. 4th ed. Moscow: Medicine, 1989. 335 p. (In Russian).
12. Tomayko M., Reynolds P. Determination of subcutaneous tumor size in athymic (nude) mice. Cancer Chemotherapy and Pharmacology, 1989; 24(3): 148–154.
13. Toyokuni S., Okamoto K., Yodoi J., Hiai H. Persistent oxidative stress in cancer. FEBS Letters, 1995; 358: 1–3.
14. White N., Gillian K., Butler P., Burnstock G. An in vivo model of melanoma: treatment with ATP. Purinergic Signal, 2009; 5(3): 327–333.
15. Wittgen H.G., Van Kempen L.C. Reactive oxygen species in melanoma and its therapeutic implications. Melanoma Res, 2007; 17: 400–9.
16. Zhang X., Teodorro J., Nadeau Jay. Intratumoral gold-doxorubicin is effective in treating melanoma in mice. Nanomedicine: Nanotechnology, Biology, and Medicine, 2015; 20: 1–11.
STUDY OF INHIBITION OF B16F10 MELANOMA GROWTH IN MICE BY LANDOMYCIN A IN COMPARISON TO DOXORUBICIN

ISSN 1996-4536 (print) • ISSN 2311-0783 (on-line) • Біологічні Студії / Studia Biologica • 2016 • Том 10/№1 • С. 5–16

ДОСЛІДЖЕННЯ ІНГІБУВАННЯ РОСТУ МЕЛАНОМИ B16F10 ЛАНДОМІЦИНОМ А ПОРІВНЯНО З ДОКСОРУБІЦІНОМ У МИШЕЙ

Л. В. Легка1, Р. Р. Панчук1, Н. Р. Скорохід1, Ю. С. Козак2, Ю. Рор2, Р. С. Стойка1,3

1Інститут біології клітини НАН України, вул. Драгоманова, 14/16, Львів 79005, Україна e-mail: lilyalehka@gmail.com
2Відділ фармацевтичних наук, Фармацевтичний коледж, Університет Кентуккі вул. Лаймстоун, 789 S, Лексінетон, Кентуккі 40536-0596, США
3Львівський національний університет імені Івана Франка вул. Грушевського, 4, Львів 79005, Україна

Ландоміцин А – новий антибіотик ангуциклінового ряду з антинеопластичною активністю щодо пухлинних клітин різного ґенезу. У цій роботі ми досліджували вплив ландоміцину А на ріст мишачої меланоми лінії B16F10. Було з’ясовано, що досліджуваний антибіотик має виражену дозові залежну цитотоксичну активність щодо клітин цієї лінії in vitro зі значенням LC_{95} 2 мкМ, що є у 5 разів нижчим, ніж для протипухлинного антибіотика доксорубіцину, який широко використовують для лікування солідних пухлин. Ландоміцин А у дозі 10 мг/кг маси тіла не спричиняв паходомічних змін, смертності або симптомів токсичності в інтактних мишей лінії C57black/6. Не спостерігали істотних змін ваги та гематологічних показників у тварин, яким вводили ландоміцин А, порівняно з тваринами контрольної групи. Не зважаючи на те, що для B16F10 меланоми in vivo характерний швидкий ріст і постійне збільшення об’єму пухлин, ландоміцин А ефективно пригнічував ріст пухлини без вираженого мієлосупресивного ефекту, кардіо- і гепатотоксичності, які властиві доксорубіцину. Отримані результати доводять перспективність застосування ландоміцину А в хіміотерапії злоякісних пухлин.

Ключові слова: ландоміцин А, меланома, об’єм пухлини, оксидативна терапія.

ИССЛЕДОВАНИЕ ИНГИБИРОВАНИЯ РОСТА МЕЛАНОМЫ B16F10 ЛАНДОМИЦИНОМ А ПО СРАВНЕНИЮ С ДОКСОРУБИЦИНОМ У МЫШЕЙ

Л. В. Легка1, Р. Р. Панчук1, Н. Р. Скорохід1, Ю. С. Козак2, Ю. Рор2, Р. С. Стойка1,3

1Институт биологии клетки, НАН Украины, ул. Драгоманова, 14/16, Львов 79005, Украина e-mail: lilyalehka@gmail.com
2Отдел фармацевтических наук, Фармацевтический колледж, Университет Кентукки ул. Лаймстоун, 789 S, Лексингтон, Кентукки 40536-0596, США
3Львовский национальный университет имени Ивана Франко ул. Грушевского, 4, Львов 79005, Украина

Ландомицин А – новый антибиотик ангуциклинового ряда с антинеопластической активностью в отношении опухолевых клеток различного генеза. В этой работе мы исследовали влияние ландомицина А на рост мышиной меланомы линии B16F10. Было выяснено, что исследуемый антибиотик имеет выраженную дозозависимую цитотоксическую активность на этой линии клеток in vitro со значением

ISSN 1996-4536 (print) • ISSN 2311-0783 (on-line) • Біологічні Студії / Studia Biologica • 2016 • Том 10/№1 • С. 5–16
ЛС₅₀ 2 мкм, що в 5 раз нижче, ніж для доксорубіцина, протистатичного антибіотика, який широко використовують для лікування солідних опухолей. Ландомицин А в дозі 10 мг/кг маси тіла не вызвав патологічних змін, смертності або симптомів токсичності у інтактних мишей лінії C57black/6. Не замітили суттєвих змін ваги та гематологічних показників у тварин, які вводили ландомицин А, по порівнянню з тваринами контрольної групи. Не- доторгуючи на це, для B16F10 меланоми in vivo характерний швидкий рост і постійне збільшення об'єму опухолі, ландомицин А ефективно підавляв рост опухолі без вираженого міелосупресивного ефекту, кардіо- та гепатотоксичності, які звичайні для доксорубіцина. Одержані результати доказують перспективність використання ландомицина А в хіміотерапії злакачествених опухолей.

Ключеві слова: ландомицин А, меланома, об'єм опухолі, оксидативна терапія.