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EFFECT OF A NOVEL THIAZOLE DERIVATIVE AND COMPLEX WITH POLYMERIC CARRIERS ON THE PROCESSES OF LIPID PEROXIDATION IN LYMPHOMA CELLS

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Background. Many types of tumors are sensitive to changes in prooxidant-antioxidant balance. Thus, further studies on reactive oxygen species inducing antitumor drugs that generate oxidative stress-dependent cytotoxic effects are promising. Our previous works showed that thiazole derivatives in combination with polymeric carriers have a pronounced cytotoxic effect on tumor, while not being cytotoxic against pseudo-normal cells *in vitro*. It was found that thiazole derivatives in complex with PEG-based polymeric carriers affected the antioxidant system of lymphoma cells *in vitro*. The aim of this work was to study the *in vitro* effect of the complex of thiazole derivative *N*-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) in combination with polymeric carriers poly(VEP-*co*-GMA)-*graft*-mPEG (Th1), poly(PEGMA) (Th3) and poly(PEGMA-*co*-DMM) (Th5) on the level of lipid peroxidation products in NK/Ly cells.

Materials and Methods. The experiments were conducted on white wild-type male mice with a grafted NK/Ly lymphoma. Ascites tumor cells were inoculated into mice intraperitoneally. Abdominal drainage with ascites of anesthetized mice was performed with a sterile syringe on the 7th–10th days after inoculation. Investigated compounds BF1, polymeric carriers Th1, Th3, Th5 and combination of BF1 + Th1 (Th2), BF1 + Th3 (Th4) and BF1 + Th5 (Th6) at a final concentration of 10 μM were added to the lymphoma samples and incubated for 10 minutes. The level of lipid peroxidation products, such as lipid hydroperoxides and thiobarbituric acid-positive products) were determined according to the techniques described below.

Results. All applied complexes based on thiazole derivative BF1 and PEG-based polymeric carriers at a concentration of 10 μM increased the activity of lipid hydroperoxides in the lymphoma cells by 29–36% compared to control. Complexes Th2 and Th6 increased the significance of BF1 influence on lymphoma cells from $P < 0.05$ to $P < 0.01$. Among all of the studied complexes, Th4 and Th6 significantly increased the level of TBA-positive products, while Th2 and BF1 did not change the content of the secondary products of lipid peroxidation. None of the unconjugated polymeric carriers affected the level of lipid peroxidation products.

Conclusions. Thus, based on the results of this work, thiazole derivative BF1 in complex with polymeric carriers increases the level of primary and secondary products of lipid peroxidation in lymphoma cells. Polymeric carriers enhanced the effect of thiazole derivative on the studied parameters, so complexes of thiazole derivatives and PEG-containing polymeric carriers should be taken into consideration and further investigated as potential antitumor agents.

Keywords: lymphoma, thiazole derivative, polymeric carriers, polyethyleneglycol, lipid peroxidation

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INTRODUCTION

Many problems of cancer chemotherapy are based on adaptive responses of tumor cells to oxidative stress, hypoxia and DNA damage that allow the cells to exist and grow under adverse conditions and acquire therapeutic resistance (Chern & Tai, 2020). It was found that these adaptive responses are crucial for tumorigenesis, cancer cells survival and progression (Cubillos-Ruiz, Bettigole & Glimcher, 2017). The generation of reactive oxygen species (ROS) is a typical biochemical mechanism of cancer cells survival. ROS react with polyunsaturated fatty acids of cellular membranes, which leads to the activation of lipid peroxidation (LPO) and to the creation of a wide variety of oxidative products. Each of these groups of products characterizes the intensity of LPO and the degree of damage to lipids, amino acids and nucleic acids. Besides the role of ROS in tumorigenesis, an increased ROS level and other primary and secondary products of LPO, such as lipid hydroperoxides, malondialdehyde (MDA) or 4-hydroxynonenal can inhibit tumor cell growth and overcome the antioxidant defense of cancer cells that lead to apoptosis (Aggarwal *et al.*, 2019; Perillo *et al.*, 2020). The development of anticancer agents with multiple cytotoxic properties including generation of oxidative stress and inhibition of antioxidant defense enzymes may help overcome the resistance of cancer cells.

It is known that thiazole derivatives, especially those with anticancer action, affect antioxidant enzymes and the production of ROS and also exert anticancer effect on different animal and human cancer cell lines, such as glioblastoma, hepatocarcinoma, melanoma, breast and lung adenocarcinomas, leukemia and lymphoma cells (Finiuk *et al.*, 2017; Shalai *et al.*, 2020). It was previously found that thiazole derivative *N*-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) affected the prooxidant-antioxidant balance. BF1 increased the activity of hydroperoxides, but there were no significant changes in the level of TBA-positive products. Ya. Shalai *et al.* (2018)

found that the level of antioxidant defense system changed due to an increased activity of superoxide dismutase, while the activity of catalase and glutathione peroxidase were reduced (Shalai *et al.*, 2019; 2020).

Among the major limitations on clinical use of thiazole derivatives are their low water solubility, which significantly decrease their efficacy, and the difficulty of their delivery to the target tissue. Encapsulation, combination and entrapment of anticancer agents with polymeric carriers enhance their transport to the tumor tissue, inhibit their rapid biodegradation and increase their bioavailability, provide a longer circulation half-life of drugs, improve their efficacy and allow to decrease a dose of application (Bahrami *et al.*, 2017; Parveen, Arjmand & Tabassum, 2019).

As previously established, thiazole derivative BF1 in complex with polymeric carriers based on polyethylene glycol (PEG) changed the activity of antioxidant enzymes causing an apoptotic-like transformations in lymphoma cells (Popovych *et al.*, 2021) and exhibited a higher level of cytotoxicity towards specific tumor cell lines than the unconjugated thiazole derivative or/and well known chemotherapeutic agent doxorubicin (Finiuk *et al.*, 2021).

Therefore, the aim of the present study was to evaluate the impact of thiazole derivative BF1 conjugated with PEG-based polymer carriers on primary and secondary products of lipid peroxidation.

MATERIALS AND METHODS

All experiments were performed on white wild-type male mice with a grafted NK/Ly lymphoma (n = 10; body weigth 20–30 g). Manipulations with animals were carried out under the principles of the “General Ethical Principles of Experimentation on Animals” approved by the First National Congress on Bioethics (Kyiv, Ukraine, 2001) and “European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes” (Strasbourg, France, 1985) as well as approved by the Ethics Committee of Ivan Franko National University of Lviv, Ukraine at the beginning of the research (Protocol No 17-02-2021 of 09.02.2021) and after the completion of the study (Protocol No 17-12-2022 of 01.02.2022). Mice were housed in a standard vivarium under typical laboratory conditions with constant temperature on a mixed ration.

To initiate the mouse lymphoma tumor 0.15–0.2 mL of ascite of (15–20 · 10^6 of NK/Ly cells) were injected intraperitonealy. The abdominal drainage of ascite was performed from anaesthetized mice with sterile syringe on 9–12 day after the inoculation.

The initial 10 μM solution of thiazole derivative BF1 (full name: N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide) was synthesized at the Department of Organic Chemistry of Ivan Franko National University of Lviv and the PEGcontaining carriers (poly(VEP-*co*-GMA)-graft-mPEG (Th1), poly(PEGMA) (Th3) and poly(PEGMA-*co*-DMM) (Th5)) were synthesized at the Department of Organic Chemistry of the Lviv Polytechnic National University, as described earlier (Mitina *et al.*, 2020; Finiuk *et al.*, 2017).

Water dispersions of polymeric carriers (PC) – Th1, Th3 and Th5 and their complexes with the BF1 derivative were dissolved in dimethyl sulfoxide (DMSO) and the solutions were subsequently transferred in water (Th2, Th4, Th6).

Three experimental groups of chemical compounds were prepared: the 1st group – BF1 (10 μM), Th1 (1 g/100 mL) and Th2 (Th1 (1 g/100 mL)) + BF1 (0.03 g/100 mL), the 2nd group – BF1 (10 μM), Th3 (1 g/100 mL) and Th4 (Th3 (1 g/100 mL)) + BF1

(0.03 g/100 mL), and the 3rd group – BF1 (10 μM), Th5 (1 g/100 mL) and Th6 (Th5 (1 g/100 mL)) + BF1 (0.03 g/100 mL). The lymphoma homogenate was incubated for 10 min with each of the compounds (BF1, PC or BF1 + PC). Please, see other experimental explanations in the **Table**.

Table. **Scheme of control and experimental groups used in the project**

Name of sample	Thiazole derivative	Polymeric carrier	Complex of thiazole derivative and polymeric carrier
Control	-	-	-
BF1	+	-	-
Th1, Th3, Th5	-	+	-
Th2, Th4, Th6	-	-	+

To measure the activity of lipid hydroperoxides and TBA-positive products, lymphoma cell samples were frozen in a freezer chamber to -20 °C and subsequently used for investigation.

The level of lipid hydroperoxides in the homogenate of lymphoma was determined by the method based on precipitation of the protein with trichloroacetic acid, followed by the addition of ammonium thiocyanate and was expressed in conventional units/min · mg of protein (Myronchyk, 1984). The content of TBA-positive products was evaluated according to the amount of formed malonic dialdehyde (MDA) (Timirbulatov & Seleznev, 1981). The content of MDA is presented in μmoles/mg of protein. Protein concentration in every sample was determined by the method of O. Lowry *et al.* (Lowry, Rosebrough, Farr, & Randall, 1951).

The statistical analysis of the results was made and illustrated using MS Excel-2013 and Statistica programs. All experiments were repeated 5 times in each variant. All data are presented as a mean ± SD. To determine statistically significant differences between the means of independent investigation groups, the one-way analysis of variance (ANOVA) was used. Statistical analyses were performed using *t*-test. *P* values below 0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

Figure 1 shows the changes in the content of primary lipid oxidation products (hydroperoxides) in lymphoma under the action of BF1, PCs and complexes of BF1 with PCs. Control levels of hydroperoxides was ~ 0.023–0.029 conventional units/mg of protein. It was found that the level of primary products of lipid oxidation in lymphoma cells under the action of BF1 at a concentration of 10 μM in three series of experiments increased by 21%, 17% and 22% (P <0.01), respectively (**Fig. 1*A*, 1*B*, 1*C***). PCs Th1, Th3, Th5 did not affect the level of hydroperoxides in lymphoma cells. Complex Th2 (BF1 + Th1) at a concentration of 10 μM increased the level of hydroperoxides by 31% (P <0.01) (**Fig. 1*A***). The level of primary lipid oxidation products increased under the action of complex Th4 (BF1 + Th3) at 36% (P <0.05) (**Fig. 1*B***). Complex Th6 (BF1 + Th5) increased the level of hydroperoxides by 29% (P <0.01) (**Fig. 1*C***). It is noteworthy that a more significant influence was noticed under the action of complexes Th2 and Th6 compared to unconjugated BF1 effect.

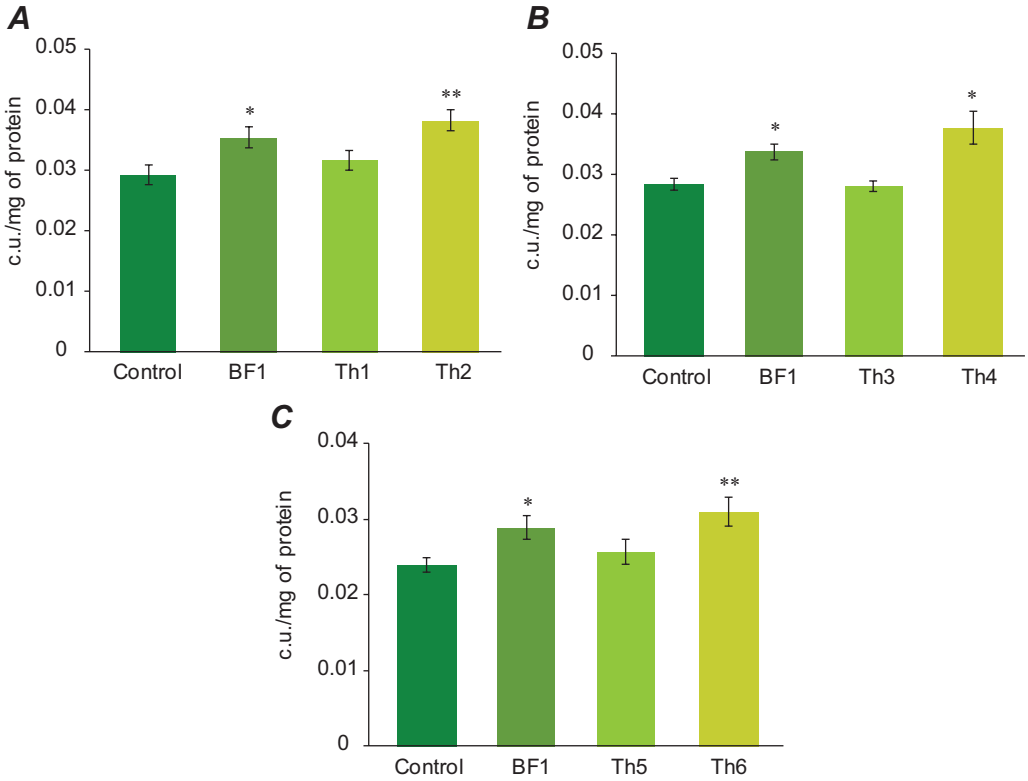

Fig. 1. Effect of the thiazole derivative (BF1), unconjugated polymeric carriers (Th1, Th3, Th5) and complexes of BF1 with PCs (Th2, Th4 and Th6) on the level of hydroperoxides in the lymphoma cells. Panel A represents the effects of BF1, the unconjugated polymer based on poly(VEP-*co*-GMA)-graft-mPEG (Th1) and its complex with BF1 (Th2) compared to control. Panel B represents the effects of BF1, the unconjugated polymer based on poly(PEGMA) (Th3) and its complexes with BF1 (Th4) compared to control. Panel C represents the effects of BF1, the unconjugated polymer based on poly(PEGMA-*co*-DMM) (Th5) and its complex with BF1 (Th6) compared to control. M ± m; n = 5. * – P<0.05; ** – P<0.01

Figure 2 shows the changes in the content of secondary products of lipid peroxidation (TBA-positive products) in lymphoma under the action of BF1, polymeric carriers (PCs) and complexes of BF1 with PCs. Control levels of TBA-positive products were ~ 0.048–0.061 conventional units / mg of protein. Compound BF1 at a concentration of 10 μM did not affect the level of TBA-positive products in lymphoma cells in three series of experiments (**Fig. 2*A*, 2*B*, 2*C***). Unconjugated PCs Th1, Th3, Th5 and complex Th2 did not change the level of secondary products either. It was found that complex Th4 increased the level of TBA-positive products by 14% (P <0.01) (**Fig. 2*B***). The level of TBA-positive products also increased under the action of complex Th6 by 18%.

New technologies for tumor treatment are aimed at developing substances that effectively inhibit or delay carcinogenesis (Baraldi *et al.*, 2012) by selectively increasing antioxidant potential (Khan, Afaq & Mukhtar, 2008) and inducing apoptosis of tumor cells (Paliwal, Sundaram & Mitragotri, 2005). Special attention is paid to drugs that can prevent the metastasis of primary sources of carcinogenesis (Narang & Desai, 2009). Among the difficulties encountered in the treatment of cancer are the physico-chemical

properties of the potential of chemotherapeutic agents, such as low water solubility and low stability, leading to poor efficacy. Targeting drugs or pharmaceutical compounds to tumor site increases cancer treatment efficiency and therapeutic outcome. Nanoparticles (NPs) based on PEG are unique delivery systems for site-targeting within an organism. Many novel technologies have been established in many drug studies (Bayram, Ozgur, Tutar & Tutar, 2018). Advantages of polymeric NPs as drug carriers include their potential use for controlled release, the ability to protect drug and other molecules with biological activity (Zielińska *et al.*, 2020).

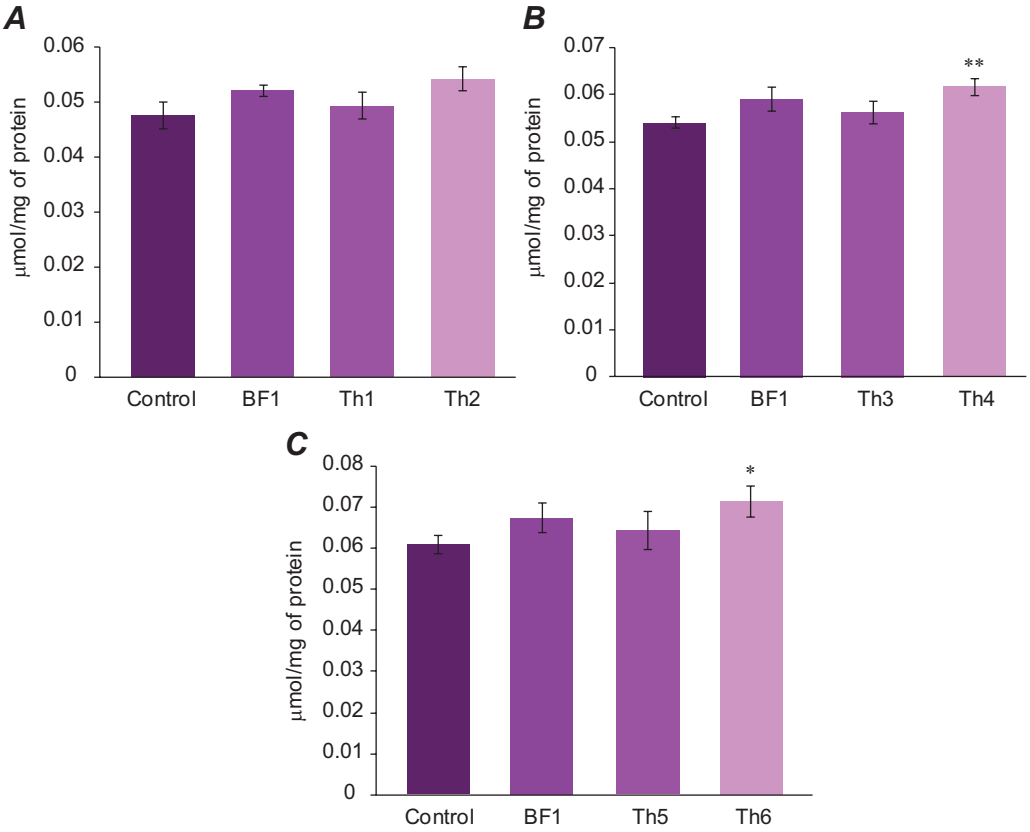

Fig. 2. Effect of the thiazole derivative (BF1), unconjugated polymeric carriers (Th1, Th3, Th5) and complex of BF1 with PCs (Th2, Th4 and Th6) on the level of TBA-positive products in the lymphoma cells. Panel A represents the effects of BF1, the unconjugated polymer based on poly(VEP-*co*-GMA)-graft-mPEG (Th1) and its complex with BF1 (Th2) compared to control. Panel B represents the effects of BF1, the unconjugated polymer based on poly(PEGMA) (Th3) and its complexes with BF1 (Th4) compared to control. Panel C represents the effects of BF1, the unconjugated polymer based on poly(PEGMA-*co*-DMM) (Th5) and its complex with BF1 (Th6) compared to control. M ± m; n = 5. * – $P<0.05$; ** – $P<0.01$

In our previous study, we found that BF1 in different concentrations increased the level of hydroperoxides (Shalai *et al.*, 2018). In this study, we also recorded an increase in the level of primary products under the action of the BF1 in concentration 10 µM. This concentration was chosen based on the more prominent antitumor BF1 actions,

such as cytotoxicity, ultrastructure changes and antioxidant defense system compared to BF1 in concentrations 1 and 50 μM. In addition, the level of hydroperoxides incrased under the action of complexes with BF1 and PCs. PEG-PCs improved the significance of BF1 influence on the level of hydroperoxides in NK/Ly cells compared to unconjugated thiazole derivative from $P < 0.05$ to $P < 0.01$. Earlier we found that the studied compounds affected the activity of enzymes of the antioxidant defense system in lymphoma cells (Popovych *et al.*, 2021). Therefore, we consider that changes in the level of primary products of LPO directly depend on changes in antioxidant enzyme activities.

It should be noted, that BF1 alone did not affect the level of TBA-positive products in lymphoma cells (Shalai *et al.*, 2018), while the investigated complexes of BF1 with PCs (Th4 and Th6) significantly increased the level of these LPO products. Therefore, polymeric carriers have improved the effect of BF1 on LPO processes in lymphoma cells.

Probably, the different effects of BF1 on primary and secondary LPO products are related to the specificity of the methods used in the work. Thus, the classical method of measuring secondary products of LPO (Timirbulatov and Seleznev, 1981) allows measuring the main end product – MDA. However, the amount of other products of lipoperoxidation (butanal, pentanal, noneal, etc.) may also affect the BF1 action.

Phospholipid-peroxidation-driven form of programmed cell death has been identified and extensive evidence has been found to support its importance in a variety of pathological processes (Dixon *et al.*, 2012). Earlier we showed that the apoptotic and necrotic changes in the structure of lymphoma cells occur under the influence of thiazole derivatives (Shalai *et al.*, 2019; Popovych *et al.*, 2021). In this study, we provide evidence that LPO processes are involved in the mechanisms of these apoptotic and necrotic changes.

Thus, thiazole derivative BF1 in complex with polymeric carriers increases the level of primary and secondary products of LPO in lymphoma cells. Polymeric carriers improve the effect of the thiazole derivative on the studied parameters. These data indicate that lipid peroxidation is part of the mechanism of neutralization of tumor cells by thiazole derivatives.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: This article does not contain any studies with human subjects performed by any of the authors.

Animal studies: All international, national and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [M.V.I.]; methodology, [M.V.I.; Ya.R.Sh.]; validation, [M.V.I]; formal analysis, [M.V.I.].; investigation, [M.V.I.; Ya.R.Sh.]; resources, [M.V.I.; N.O.M; O.S.Z.]; data curation, [A.M.B.]; writing – original draft preparation, [M.V.I., Ya.R.Sh.]; writing – review and editing, [M.V.I.; Ya.R.Sh., A.M.B.]; visualization, [M.V.I.]; supervision, [A.M.B.]; project administration, [A.M.B.]; funding acquisition, [Ukrainian government grant No 0119U002201].

All authors have read and agreed to the published version of the manuscript.

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ЕФЕКТ НОВОСИНТЕЗОВАНОГО ПОХІДНОГО ТІАЗОЛУ ТА ЙОГО КОМПЛЕКСІВ З ПОЛІМЕРНИМИ НОСІЯМИ НА ПРОЦЕСИ ПЕРЕКИСНОГО ОКИСНЕННЯ ЛІПІДІВ КЛІТИН ЛІМФОМИ

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Обґрунтування. Багато пухлин чутливі до змін прооксидантно-антиоксидантного балансу, тому розробка протипухлинних препаратів, які індукують утворення активних форм кисню та генерування залежних від окисного стресу цитотоксичних продуктів, є на сьогодні актуальним. Нашими попередніми дослідженнями встановлено виражену цитотоксичну дію похідних тіазолу в поєднанні з полімерними носіями на пухлинні клітини *in vitro*. З'ясовано, що похідні тіазолу в комплексі з полімерними носіями на основі поліетиленгліколю впливають на антиоксидантну систему клітин лімфоми *in vitro*. Метою роботи було вивчення дії комплексу похідного тіазолу *N*-(5-бензил-1,3-тіазол-2-іл)-3,5-диметил-1-бензофуран-2-карбоксаміду (BF1) у поєднанні з полімерними носіями полі(VEP-*co*-GMA)-graft-mPEG (Th1), полі(PEGMA) (Th3) та полі(PEGMA-co-DMM) (Th5) на рівні продуктів перекисного окислення ліпідів лімфоми Немет–Келнера (NK/Ly) *in vitro.*

Матеріали та методи. Експерименти виконували на білих мишах самцях дикого типу з прищепленою лімфомою. Пухлинні клітини прищеплювали мишам внутрішньочеревно. Дренування черевної порожнини для забору асциту виконували стерильним шприцом під етерним наркозом на 7–10-ту добу після інокуляції. Досліджувані сполуки BF1, BF1 + Th1 (Th2, Th12), BF1 + Th3 (Th4, Th14), BF1 + Th5 (Th6, Th16) у кінцевій концентрації 10мкМ додавали до дослідних зразків, інкубували впродовж 10 хв, а рівень продуктів перекисного окиснення ліпідів (гідропероксидів ліпідів і позитивних продуктів тіобарбітурової кислоти) визначали згідно з класичними методиками.

Результати. Усі досліджувані комплекси на основі похідного тіазолу BF1 та полімерних носіїв на основі поліетиленгліколю у концентрації 10 мкМ підвищували активність гідропероксидів ліпідів у клітинах лімфоми на 29–36 % порівняно з контролем. Серед усіх досліджуваних комплексів Th4 і Th6 суттєво підвищували рівень ТБК-позитивних продуктів, тоді як Th2 і вільний BF1 не змінювали вміст цих вторинних продуктів. Жоден із вільних полімерних носіїв не впливав на рівень продуктів перекисного окиснення ліпідів.

Висновки. Ґрунтуючись на результатах досліджень, встановлено, що похідне тіазолу BF1 у комплексі з полімерними носіями підвищує рівень первинних і вторинних продуктів ПОЛ у клітинах лімфоми. Полімерні носії посилювали вплив похідного тіазолу на досліджувані параметри, тому комплекси похідного тіазолу та поліетиленгліколь-вмісних полімерних носіїв можуть бути використані для подальших досліджень як потенційні протипухлинні засоби.

Ключові слова: лімфома, похідне тіазолу, полімерні носії, поліетиленгліколь, перекисне окиснення ліпідів

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