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Activity of antioxidant enzymes in hepatocytes of mice with lymphoma under the action of thiazole derivative in complex with polymeric nanocarrier

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Many chemotherapeutics drugs have low water solubility, which potentially can decrease their anticancer potential. The use of drug delivery systems has proven to be highly effective in addressing the challenges associated with delivering hydrophobic chemotherapy drugs to tumor tissues. However, two major issues that arise in the clinical nanoparticle-based treatment of cancer are hepatotoxicity and suppression of the hematopoietic system, which can limit their medical applicability. As previously established, thiazole derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide in complex with polymeric nanocarriers (nanomicelles) based on polyethylene glycol exhibited a greater level of cytotoxicity towards specific tumor cell lines melanoma, glioblastoma, hepatocarcinoma, leukemia, etc. This compound and its complexes with polymeric nanomicelle significantly changed the activity of antioxidant enzymes in lymphoma cells. Therefore, the purpose of this study was to examine the impact of a thiazole derivative with polymeric nanomicelles based on polyethylene glycol on the hepatocytes (liver cells) of mice that had been implanted with Nemet-Kelner lymphoma. The investigated compounds thiazole derivative, polymeric nanomicelle, and combination of thiazole derivative with nanomicelle at a final concentration of 10 μM were added to the liver samples and incubated for 10 min. The activity of antioxidant defense system enzymes such as superoxiddismutase, catalase, glutathionperoxidase was determined in liver homogenate under the action of studied compounds *in vitro*. It was reported that neither thiazole derivative, nanomicelle, nor their complex changed the activity of antioxidant enzymes in hepatocytes from mice with lymphoma. Thiazole derivative and it complex with nanomicelle had limited negative side effects in the mice with lymphoma. The investigated compounds were not hepatotoxic toward murine liver cells.

Key words: antitumor drugs, nanomicelle, hepatotoxicity, antioxidant system

Introduction

In the ever-evolving battle against cancer, the development of powerful chemotherapeutics anticancer drugs has been an instrument for extending survival rates and improving the life quality for countless patients. While these potential anticancer agents hold potential in targeting malignant cells, their impact on healthy tissues cannot be overlooked. Among the vital organs affected, the liver, the central organ in both metabolism and detoxification,

stands particularly vulnerable [10, 18]. Understanding the complicated interaction between anticancer drugs and liver cells is crucial for optimizing treatment strategies and minimizing potential side effects. Different chemotherapeutic anticancer drugs can have varying effects on healthy liver cells. Anthracycline drugs, such as *Doxorubicin* and *Daunorubicin*, are widely used in cancer treatment but can lead to hepatocellular injury, causing hepatocyte damage and impairing liver function [18, 21]. The mechanism of toxicity involves the generation of reactive oxygen species (ROS) and interference with mitochondrial function. Taxanes, such as *Paclitaxel* and *Docetaxel*, can lead to hepatocellular injury, resulting in liver enzyme elevations and hepatotoxicity [14, 21]. The underlying mechanisms involve interference with microtubule function and disruption of cell division. Tyrosine kinase inhibitors, such as *Sorafenib* and *Imatinib*, have a more selective mechanism of action compared to traditional chemotherapy, but they also can cause hepatotoxicity, including elevated liver enzymes activity and hepatic steatosis [1, 21]. Overall, the impact of chemotherapeutic anticancer drugs on healthy liver cells can vary depending on the specific drug and individual factors. Understanding these effects is crucial for oncology to optimize treatment regimens, manage potential liver toxicity, and provide supportive care to patients undergoing cancer treatment.

Previous studies have demonstrated that thiazole N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) possesses a significant level of toxicity towards some tumor cell lines, while exhibiting no destructive effects on pseudonormal cell lines and hepatocytes in NK/Ly mice [8, 19]. The possible anticancer mechanism of action of the thiazole derivative based on the generation of a large number of ROS, which triggers a cascade of reactions in tumor cells that lead to their apoptosis [11].

However, BF1, like many chemotherapeutics drugs, has low water solubility, which potentially can decrease its anticancer potential. Nanomicelles, also known as polymeric micelles, are self-assembled nanostructures composed of amphiphilic block copolymers. These nanoscale structures have a hydrophilic outer shell and a hydrophobic core [2]. The unique structure of nanomicelles enables them to encapsulate hydrophobic anticancer drugs within their hydrophobic core, thereby increasing the solubility of these drugs. Thus, nanomicelles serve as effective drug delivery vehicles by encapsulating hydrophobic anticancer drugs, improving their solubility, stability, and targeted delivery to tumor tissues [16, 20]. This approach holds great promise for enhancing the therapeutic efficacy of anticancer drugs and reducing their side effects.

As previously established, thiazole derivative BF1 in complex with polymeric nanomicelles based on polyethylene glycol (PEG) poly(PEGMA) (Th3) exhibited a greater level of cytotoxicity towards specific tumor cell lines compare to unconjugated BF1 or/and chemotherapeutic drug *Doxorubicin* and lead to apoptotic-like changes in lymphoma cells [9].

It is important to note that nanomicelles can interact with liver cells through several mechanisms, which can impact their function and overall cellular response [4]. Nanomicelles can be internalized by liver cells through endocytosis or receptor-mediated pathways. The nanomicelles can influence the intracellular environment and signaling pathways within liver cells. On the other hand, nanomicelles can trigger cellular responses in liver cells. Depending on their composition and properties, they can activate signaling pathways, induce inflammatory responses, or affect gene expression within the cells [5]. These responses can influence cellular functions and may have implications for liver health and toxicity.

The aim this work was to study the effect of thiazole derivative BF1 in complex with PEG-based nanomicelles (Th3) on the prooxidant-antioxidant balance in hepatocytes of mice with grafted NK/Ly.

Materials and methods

All experiments were performed on white wild-type male mice with a grafted NK/Ly lymphoma (n=10; body weight 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 from 09.02.2021) and after the completion of the study (Protocol no. 12-05-2023 from 5.05.2023). 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 ($15–20\times10^6$ of NK/Ly cells) were injected intraperitoneally. To extirpate the liver, the animals were decapitated under ether anesthesia, after which the organ was quickly excised. After removal, the liver was weighed and washed from blood with a cooled solution of the following composition (in mM): NaCl — 140, KCl — 4.7, $MgCl_2$ — 1, glucose — 5, HEPES — 10; pH 7.4. The liver was crushed using a metal press, solution was added in the ratio of 8 ml of solution per 1 g of tissue, and cells were destroyed in a Potter-Evelheim homogenizer at 800 rpm. The initial 10 μM solution of thiazole derivative BF1 was synthesized at the Department of Organic Chemistry of Ivan Franko National University of Lviv and the homopolymer of PEG-methacrylate with a molecular weight of the PEG-unit 475 kDa (poly(PEGMA) (Th3)) were synthesized at the Department of Organic Chemistry of the Lviv Polytechnic National University, as described earlier [8, 15]. Water dispersions of polymeric nanomicelle (PN) — Th3 and its complex with the BF1 (Th4) derivative was dissolved in dimethyl sulfoxide (DMSO) and the solutions were subsequently transferred in water.

Catalase (CAT) activity was measured by the method of Hamza et al. [7] with an absorption wavelength of 410 nm and was expressed in nmoles of H_2O_2/min×mg of protein. Superoxide dismutase (SOD) activity was measured by the method of Paoletti et al. [17] and was expressed as unit active/min×mg protein. Glutathione peroxidase (GPx) activity was measured by the method of Hadwan et al. [6] with an absorption wave length of 412 nm and was expressed in G–SH/min×mg of protein. Protein concentration in every sample was determined by the method of O. Lowry et al. [13].

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

Since the redox balance in the cells of the body significantly changes during the development of a tumor, a change in the antioxidant enzymes activity should be expected. Therefore, the superoxide dismutase in the liver cells of a tumor-bearing mouse was investigated. Fig. 1 shows the changes in the SOD activity under the action of BF1, nanomicelle Th3 and complex Th3 with BF1 (Th4). Control levels of the enzyme activity in the liver of tumor-bearing mice were 5.9±0.85 units active/min×mg protein. Under the action of tested compounds, the enzyme activity in the liver of tumor-bearing mice did not change.

Because H_2O_2 is the product of SOD activity, the normal functioning of other enzymes that neutralize hydrogen peroxide is important. Therefore, we tested the effect of the studied compounds on the activity of CAT and GPO. Fig. 2 shows the changes in catalase activity under the action of BF1, nanomicelle Th3 and complex Th3 with BF1 (Th4). Control levels of enzyme activity in the liver of tumor-bearing mice were 14±1.4 nmol H_2O_2/min×mg protein. Tested compounds did not change the activity of the enzyme.

Disposing of the increased amount of H_2O_2, in addition to the CAT, is also carried out by the GPx. This enzyme has a greater affinity for hydrogen peroxide than CAT. GPx functions more efficiently at low H_2O_2 concentrations, while CAT is more efficient at high substrate concentrations during the development of oxidative stress.

Fig. 3 shows the changes in GPx activity under the action of BF1, nanomicelle Th3 and complex Th3 with BF1 (Th4). Control levels of GPx activity in the liver of tumor-bearing mice were 8.1±0.7 nmol GSH/min×mg protein. Under the action of both tested compounds, the activity of the enzyme in the liver of tumor-bearing mice did not change.

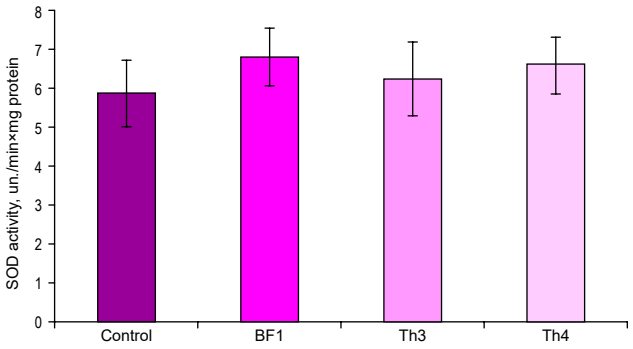

Fig. 1. The level of SOD activity in the liver of tumor-bearing mice under the action of thiazole derivative BF1, polymeric nanomicelle Th3 and complex of BF1 with Th3 (Th4) (M±m, n=5)

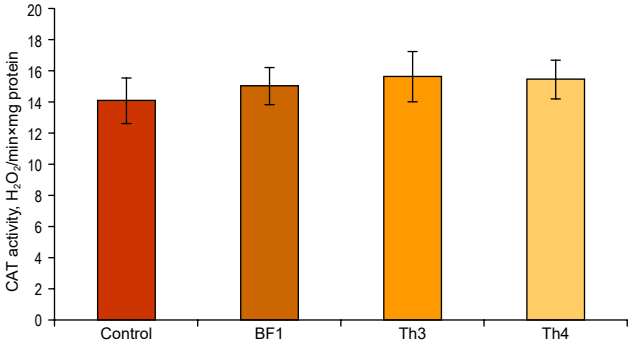

Fig. 2. The level of CAT activity in the liver of tumor-bearing mice under the action of thiazole derivative BF1, polymeric nanomicelle Th3 and complex of BF1 with Th3 (Th4) (M±m, n=5)

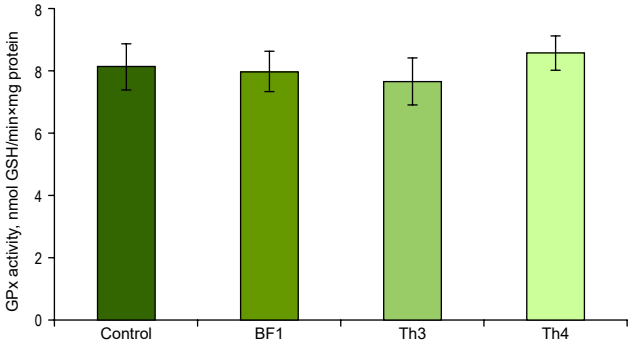

Fig. 3. The level of GPx activity in the liver of tumor-bearing mice under the action of thiazole derivative BF1, polymeric nanomicelle Th3 and complex of BF1 with Th3 (Th4) (M±m, n=5)

One of the main problems of chemotherapy treatment is side effects, when anticancer drugs negatively affect healthy cells, in particular, hepatocytes. Since the liver is the main detoxifying organ in humans and animals and plays an important role in the elimination of drugs from the body, changes in the antioxidant processes of in liver cells due to the action of newly synthesized antitumor substances may indicate negative side effects that often occur due to use of such substances.

Many chemotherapeutic drugs have a low selective effect and therefore provoke significant side effects.

Side effects of cytostatics, such as cardiotoxicity, hepatotoxicity, neurotoxicity, nephrotoxicity, and effects on the immune system are especially dangerous. The effect on the liver of antitumor substances can significantly damage the functioning of the organ and the body.

It was previously established that thiazole derivative BF1 and its complexes with PNs significantly changed the activity of antioxidant enzymes in lymphoma cells [11]. In particular, the activity of SOD increased, while the activity of CAT and GPx decreased. Such changes indicate an imbalance of enzyme activity in cancer cells under the action of antitumor substances. Therefore, antioxidant processes are involved in the mechanism of action of BF1 in a complex with polymer carriers. Interestingly, it was the complex Th4 that demonstrated the greatest effect. Therefore, it was important to investigate the effect of the studied compounds on the antioxidant enzymes activity in liver cells.

Hepatotoxicity, a commonly observed clinical manifestation associated with various anticancer treatments such as chemotherapy [10], is often accompanied by the accumulation of certain nanomaterials in the liver, leading to liver injury [21]. The primary manifestation of toxicity observed in cells or animal models exposed to different therapeutic drugs and nanomaterials is the induction of oxidative stress, which disrupts the balance between prooxidants and antioxidants [21].

A study conducted on murine hepatocytes revealed that the thiazole derivative BF1 did not induce oxidative stress or alter the levels of primary and secondary lipid peroxidation (LPO) products, namely hydroperoxides and TBA-positive products [21]. Similarly, the administration of unconjugated PN Th3 or its complex with BF1 (Th4) did not affect the levels of LPO products in hepatocytes of mice with grafted NK/Ly tumors (data not shown). However, a decline in the activity of antioxidant enzymes such as GPx, SOD, and CAT is associated with an altered oxidative status and reduced oxidative defenses [2]. Nevertheless, it was observed that neither BF1, PN, nor their complex Th4 altered the levels of antioxidant enzymes in hepatocyte cells derived from mice with NK/Ly tumors.

Based on our data, it can be inferred that significant hepatotoxicity is unlikely to occur with the administration of the BF1+PN complex, which exhibits a more pronounced therapeutic effect compared to unconjugated BF1.

Therefore, the BF1 complex with a polymer nanomicelle, which shows toxicity to cancer cells, did not affect the activity of antioxidant enzymes in the liver cells of tumor-bearing mice *in vitro*. It is also known that these complexes were not toxic to non-tumor human kidney cell lines and keratinocytes [9]. However, further research is needed to ensure the safety of these substances. It is important to examine additional parameters, including the activity of other antioxidant enzymes and levels of peroxidation products *in vivo*, to obtain a comprehensive assessment of their effects.

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Активність антиоксидантних ензимів у гепатоцитах мишей з лімфомою за дії похідного тіазолу в комплексі з полімерним наноносієм

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Багато хіміотерапевтичних препаратів мають низьку розчинність у воді, що потенційно може знизити їхній протипухлинний потенціал. Використання систем доставки ліків виявилося високоефективним у вирішенні проблем, пов'язаних із постачанням гідрофобних хіміотерапевтичних препаратів до пухлинних тканин. Однак двома основними проблемами, які виникають за клінічного лікування раку з використанням наночастинок, є гепатотоксичність і пригнічення кровотворної системи, що може обмежити їх медичне застосування. Раніше встановлено, що похідне тіазолу N-(5-бензил-1,3-тіазол-2-іл)-3,5-диметил-1-бензофуран-2-карбоксамід у комплексі з полімерними наноносіями (наноміцелами) на основі поліетиленгліколю демонструвало підвищений рівень цитотоксичності щодо специфічних ліній пухлинних клітин меланоми, гліобластоми, гепатокарциноми, лейкозу тощо. Ця сполука та її комплекси з полімерними наноміцелами істотно змінювали активність антиоксидантних ензимів у клітинах лімфоми. Тому метою цього дослідження було вивчити вплив похідного тіазолу у комплексі з полімерними наноміцелами на основі поліетиленгліколю на гепатоцити (клітини печінки) мишей, яким було імплантовано лімфому Немет-Келнера. Клітини лімфоми Немет-Келнера прищеплювали методом внутрішньочеревної інокуляції. На 14–16-й день розвитку пухлини мишей наркотизували діетиловим ефіром, декапітували, видаляли печінку та гомогенізували. Досліджувані сполуки — похідне тіазолу, полімерна наноміцела на основі поліетиленгліколю та комплекс похідного тіазолу з наноміцелою в кінцевій концентрації 10 мкМ — додавали до зразків печінки та інкубували протягом 10 хв. У гомогенаті печінки під дією досліджуваних сполук *in vitro* визначали активність таких ензимів системи антиоксидантного захисту, як супероксиддисмутаза, каталаза, глутатіонпероксидаза. Встановлено, що ні похідне тіазолу, ні наноміцела, ні їхній комплекс не змінили активності антиоксидантних ензимів у гепатоцитах мишей з лімфомою. Похідне тіазолу та його комплекс з наноміцелами мали обмежені негативні побічні ефекти у мишей з лімфомою. Досліджувані сполуки не були гепатотоксичними щодо клітин печінки мишей.

Ключові слова: протипухлинні препарати, наноміцели, гепатотоксичність, антиоксидантна система

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