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SAFETY PROFILE OF THIAZOLE DERIVATIVE AND ITS COMPLEX WITH PEG-BASED POLYMERIC NANOPARTICLES ON LIVER AND BLOOD CELLS IN TUMOR-BEARING MICE

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Background. Drug delivery systems (DDS) have demonstrated a significant ability to overcome many of the challenges associated with the delivery of hydrophobic chemotherapeutic compounds to tumor tissues. However, hepatotoxicity and suppression of the hematopoietic system are the key problems in the clinical treatment of cancer by nanoparticle-based DDS that can limit their medical exposure. The aim of this work was to investigate the effect of thiazole derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) conjugated with PEG-based polymeric nanoparticles (PEG-PN – Th1) on the hepatocytes and blood hematological parameters of mice with grafted NK/Ly.

Materials and Methods. The experiments were conducted on white wild-type male mice with grafted NK/Ly lymphoma. Investigated compounds BF1, PEG-PN Th1, and combination of PEG-PN + BF1 (Th2) at a final concentration of 10 μM were added to the liver samples and incubated for 10 minutes. The level of lipid peroxidation products and the level of antioxidant defense system (AOS) enzymes were determined according to the techniques described below. The cytological parameters of blood were investigated after the treatment of mice with BF1 in concentrations of 10 and 20 mg/kg, PEG-PN (20 mg/kg) and Th2 complex (10 mg/kg). On the 14th day of the experiment, blood was taken from all groups and the number of erythrocytes, leukocytes and leukocyte formula were counted.

Results. It was reported that neither BF1, PEG-PN, nor their complex Th2 changed the content of lipid peroxidation products or the level of AOS enzymes in hepatocytes from mice with NK/Ly. BF1 (in concentration 10 mg/kg) and PEG-PN + BF1 complex did not change the level of murine erythrocytes compared to Doxorubicin. All investigated compounds, except free PEG-PN, significantly decreased the NK/Ly-triggered leukocytosis and increased the level of small lymphocytes. The NK/Ly lymphoma development led to an increase in the number of neutrophils, while BF1 and its complex with PEG-PN reduced it significantly.

Conclusions. BF1 and PEG-PN + BF1 complex had limited negative side effects in the mice with NK/Ly. The investigated compounds were not hepatotoxic toward murine liver cells. Both BF1 and its complex with PEG-PN did not cause any major side effects on the murine blood cells.

Keywords: thiazole derivative, polymeric nanoparticles, drug delivery system, hepatotoxicity, hematological parameters

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INTRODUCTION

Despite a significant efficacy of chemotherapy in the clinical treatment of different types of cancer, many problems and limitation factors must be solved, including decreasing cytotoxicity toward non-cancer cells, overcoming multiresistance, and improving drugs solubility and selectivity (Cheng *et al*., 2021). To address these limitations and achieve better cancer therapeutic efficiency, it is necessary to design a drug delivery system (DDS) to combine chemotherapy compounds with nanocarriers. Nanoparticle-based drug delivery systems demonstrate good pharmacokinetics, precise targeting of cancer lesions, lessen side effects of chemotherapy, and reduce drug-related resistance (Gavas, Quazi & Karpiński, 2021; Vieira, & Gamarra, 2016). There are several advantages of DDS compared to “free” chemotherapeutic drugs, which suggests that it can be utilized in cancer treatment. These include an increased permeability and improved biocompatibility enabling passage through biological barriers, maintaining better specificity, bioavailability, longer half-life period, a decrease in cytotoxicity to normal tissue, a larger loading capacity, and unique drug release patterns (Ahmed, Rehman & Tabish, 2022; Cheng et al., 2021). Polymeric NPs are especially used as DDS, which shows a promising therapeutic potential.

However, like many chemotherapeutic drugs, some nanoparticles can induce numerous side effects on the hematopoietic system, cause hepatotoxicity and cardiotoxicity.

The liver is the main organ of detoxification and is one of the organs that is most exposed to NPs. Depending on the physicochemical parameters of NPs, they can impact hepatic enzyme activities and induce inflammation, oxidative stress and genotoxicity processes (Cornu, Béduneau & Martin, 2020). Specifically, oxidative stress is frequently reported to play one of the main roles in NPs-induced hepatotoxicity. Different physicochemical properties of NPs are the main factors involved in NPs ability to cause the increased production of reactive oxygen species (ROS) and, therefore, lead to tissue oxidative damage by increasing lipid peroxidation (LPO) and reducing the level of antioxidant defense system enzymes (Bostan *et al*., 2016).

Cancer patients who receive chemotherapy commonly suffer from hematological profile alteration, including decrement of WBC count and RBC count as a result of suppressed hematopoietic stem cells and ineffective erythropoiesis (Wondimneh *et al.*, 2021). Blood is responsible for the transport of all DDS to their target tissues, and it is important that researchers confirm the compatibility of engineered complexes of NPs and chemotherapeutic agents with all cellular constituents of blood, namely erythrocytes and leukocytes (de la Harpe *et al.*, 2019).This will ensure the optimum safety of DDS and enhance its effectiveness in cancer treatment.

It was established that thiazole *N*-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) exhibited a high level of toxicity towards particular tumor cell lines, while there were no toxicity effects on pseudonormal cells lines and hepatocytes in mice with NK/Ly (Finiuk *et al.*, 2017; Shalai *et al.*, 2021). BF1 in complex with PEG-based polymeric nanoparticles (poly(VEP-*co*-GMA)-*graft*-mPEG – Th1) increased the cytotoxicity effect on tumor cancer cells, enhanced the apoptosis and ROS generation of murine NK/Ly cells compared to unconjugated BF1 (Finiuk *et al.*, 2021; Popovych *et al.*, 2021). However, the safety of BF1 in complex with PEG-PN has not been studied yet.

Thus, the purpose of this work was to investigate the effect of thiazole derivative BF1 conjugated with PEG-based polymeric nanoparticles (Th1) on the hepatocytes and blood hematological parameters 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 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 murine lymphoma tumor 0.15–0.2 mL of ascite of ($15–20 \cdot 10^6$ of NK/Ly cells) were injected intraperitoneally. 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 carrier (poly(VEP-*co*-GMA)-*graft*-mPEG (Th1)) was synthesized at the Department of Organic Chemistry of the Lviv Polytechnic National University, as described earlier (Finiuk *et al.*, 2017; Mitina *et al.*, 2020). Water dispersions of polymeric carrier – Th1 and the complex with BF1 derivative was dissolved in dimethyl sulfoxide (DMSO) and the solutions were subsequently transferred into water (Th2).

To measure the activity of lipid hydroperoxides and TBA-positive products, liver cell samples were frozen in a freezer chamber to -20 °C and subsequently used for investigation. The level of lipid hydroperoxides in the liver homogenate was determined by the method based on precipitation of the protein with trichloroacetic acid, followed by

the addition of ammonium thiocyanate (Myronchyk, 1984). The content of TBA-positive products was evaluated according to the amount of formed malonic dialdehyde (MDA) (Timirbulatov & Seleznev, 1981). Protein concentration in every sample was determined by the method of O. Lowry *et al*. (Lowri et al., 1951).

Catalase activity was measured by the method of M. A. Korolyuk *et al*. with an absorption wavelength of 410 nm (Korolyuk *et al.*, 1988). Superoxide dismutase (SOD) activity was measured by the method of V. A. Kostyuk *et al*. and was expressed as unit SOD/mg protein (Kostyuk *et al.*, 1990). Glutathione peroxidase activity was measured by the method of V. M. Moin with an absorption wave length of 412 nm (Moin, 1986).

The cytological parameters of blood were investigated after the treatment of mice with BF1 in concentrations of 10 and 20 mg/kg, PEG-PN (20 mg/kg) and Th2 complex (10 mg/kg). The drug doxorubicin was used as a positive control. Administration of the compounds began the day after tumor inoculation and drugs were administered for 10 days (8 days for doxorubicin). On the 14th day of the experiment, blood was taken from all groups and the number of erythrocytes, leukocytes and leukocyte formula were counted.

The statistical analysis of the results was made and illustrated using MS Excel-2013 and Statistica programs. All experiments were repeated five times in each variant. All data are presented as a mean ± SD. Statistical significance of the difference between groups was determined with a one-way ANOVA (Bonferroni test). P values below 0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

One of the major problems in the therapy of oncology diseases is the side effects of current clinical drugs on healthy organs of patients, in particular, cardio-, nephro- and hepatotoxicity. It is known that the liver is the main organ that provides metabolic, protective, and detoxification processes in the body (Joshi, Sodhi & Pandey, 2014; Ozer *et al.*, 2008). Therefore, it was important to investigate the processes of LPO and the AOS system and study the potential negative effects of newly synthesized compounds of thiazole derivative BF1 with PEG-based polymer nanoparticle Th1.

Figure 1 represents changes in the content of primary (hydroperoxides, **Fig. 1*A***) and secondary (TBA-positive products, **Fig. 1*B***) lipid oxidation products in the liver cells of tumor-bearing mice under the influence of thiazole derivative BF1, the PEG-PN Th1 and thiazole derivative complex with PEG-PN – Th2.

The control level of hydroperoxides in the liver cells of mice with lymphoma was 2.1±0.26 conventional units/mg of protein. It was found that neither thiazole derivative nor its complex with PEG-PN (Th2) changed the content of hydroperoxides in hepatocytes of tumor-bearing mice (**Fig. 1*A***). Thus, the studied substances do not affect the level of primary products of lipid oxidation. However, hydroperoxides can quickly enter into other redox reactions and form secondary products of lipid oxidation. Therefore, the next task of the study was to determine the content of secondary lipid oxidation products in the liver of tumor-bearing mice under the influence of the investigated compounds.

Figure 1*B* shows the changes in the content of TBA-positive products in the liver cells of tumor-bearing mice under the influence of BF1, PEG-PN and the PEG-BF1 complex. The content of TBA-positive products in the liver cells of control mice was 0.61±0.05 μmol/mg of protein. None of the studied compounds significantly changed the levels of secondary products of lipid oxidation in the liver cells of tumor-bearing mice (**Fig. 1*B***).

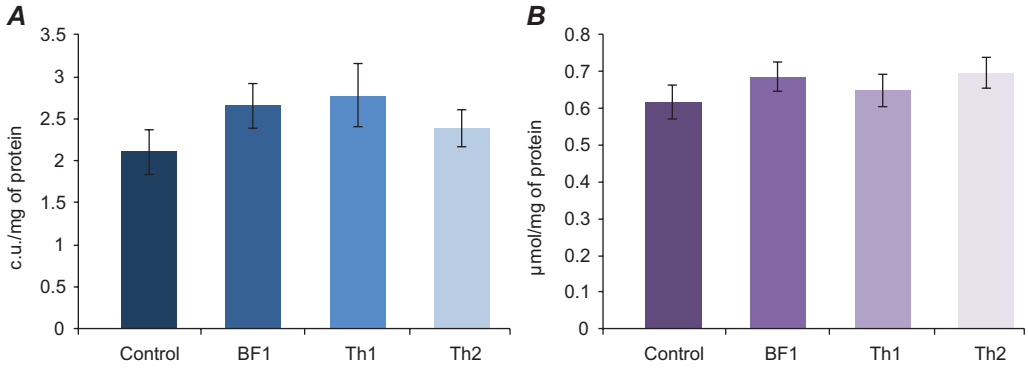

Fig. 1. Effect of thiazole derivative (BF1), unconjugated PEG-based polymeric nanoparticle (Th1) and complexes of BF1 with PEG-PN (Th2) on the level of hydroperoxides (***A***) and TBA-positive products (***B***) in the hepatocytes of tumor-bearing mice. Mean ± SD; n = 5

It was previously established that thiazole derivative BF1 and its complexes with PEG-PNs significantly changed the level of primary products of lipid oxidation and superoxide radical and, as a result, affected the enzymes of AOS in lymphoma cells. Therefore, it was important to investigate the effect of the studied compounds on the AOS enzymes in liver cells.

Figure 2 shows the changes in the activity of superoxide dismutase (SOD), catalase (CAT) and glutathionperoxidase (GPx) under the action of BF1, PEG-PN Th1 and their Th2 complex.

Control levels of enzymes in hepatocytes of tumor-bearing mice were determined: 5.57±0.74 active units/min·mg of protein for SOD (**Fig. 2*A***); 13.27±1.58 nmol H_2O_2/min·mg of protein for CAT (**Fig. 2*B***) and 7.86±0.84 nmol GSH/min×mg of protein for GPx (**Fig. 3*C***). The activity of any of the antioxidant defense system enzymes in the liver of mice with lymphoma did not significantly change under the influence of any of the investigated substances (**Fig. 2**). Thus, thiazole derivative BF1, PEG-PN Th1, and its complex Th2 did not affect the level of lipid oxidation products and the activity of antioxidant defense enzymes in the liver cells of tumor-bearing mice with NK/Ly lymphoma.

An important indicator of the chemotherapeutic drugs safety is the study of blood parameters, namely determination of the leukocyte formula and calculation of the total number of erythrocytes and leukocytes.

It was established that doxorubicin significantly caused anemia in tumor-bearing mice, reducing the number of erythrocytes by 27.6 % (6.3±0.3·10^9/mL) compared to control mice without lymphoma (8.7±0.6·10^9/mL). The studied compound BF1 at a concentration of 20 mg/kg slightly reduced the number of erythrocytes by 10.3 %, but at the concentration of 10 μM this effect was neutralized compared to control value. PEG-PN Th1 and its complexes with BF1 (Th2) did not lead to changes in the number of erythrocytes compared to the control. BF1 in both concentrations and its complex with PEG-PN significantly increased the number of erythrocytes in mice blood compared to Dox (by 26%,P ≤0.001).

Progression of NK/Ly lymphoma in mice led to leukocytosis and increased the number of lymphocytes 1.8-fold compared to these indicators in the blood of healthy animals (6.8±0.3·10^6/mL). The antitumor drug Dox significantly reduced leukocyte count

by 25 % compared to control values (P≤0.01). Unconjugated BF1 at both tested concentrations (10 and 20 mg/kg), as well as complex Th2, significantly reversed leukocytosis caused by tumor growth.

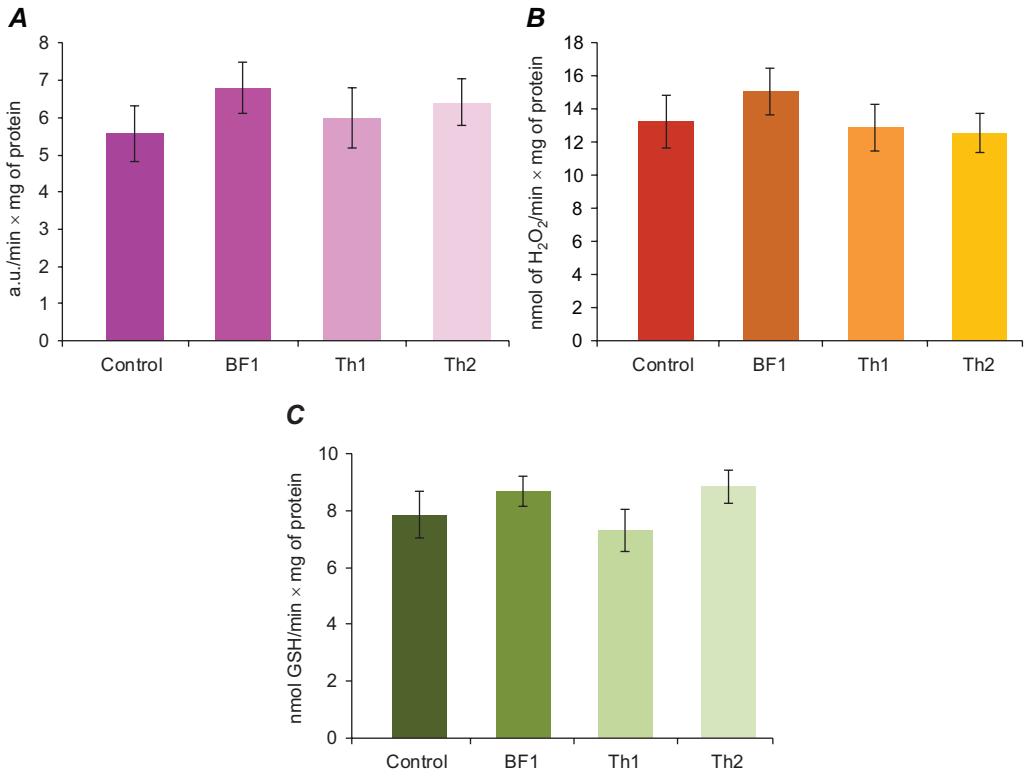

Fig. 2. Effect of thiazole derivative (BF1), unconjugated PEG-based polymeric nanoparticle (Th1) and complexes of BF1 with PEG-PN (Th2) on the activity of superoxide dismutase (***A***), catalase (***B***) and glutathionperoxidase (***C***) in the hepatocytes of tumor-bearing mice. Mean ± SD; n = 5

The next stage of the study was to analyze the percentage ratio of different types of leukocytes in tumor-bearing mice that were treated with the compounds and compare them with the ratio of lymphocytes of healthy mice and tumor-bearing mice that were not treated (**Fig. 3**). It was found that in mice with NK/Ly, the number of segmented neutrophils increased more than two-fold compared to healthy mice (57.1±2.7% and 27.9±1.8%, respectively, P ≤0.001). All studied compounds, except unconjugated PEG-PN, neutralized this effect and significantly reduced the number of segmented neutrophils compared to untreated tumor-bearing mice. However, only Dox and Th2 complex returned the number of segmented neutrophils almost to control values, while unconjugated BF1 in both concentrations slightly increased this indicator (by 29%, P ≤0.05).

Progression of NK/Ly caused an increase in a number of segmented neutrophils in the blood of tumor-bearing mice and led to a decrease in the level of small lymphocytes by 55 % compared to control animals (26.1±1.9 %, and 57.9±3.1 %, respectively, P ≤0.001). Doxorubicin, BF1 at concentrations of 10 and 20 mg/kg, and Th2 complex

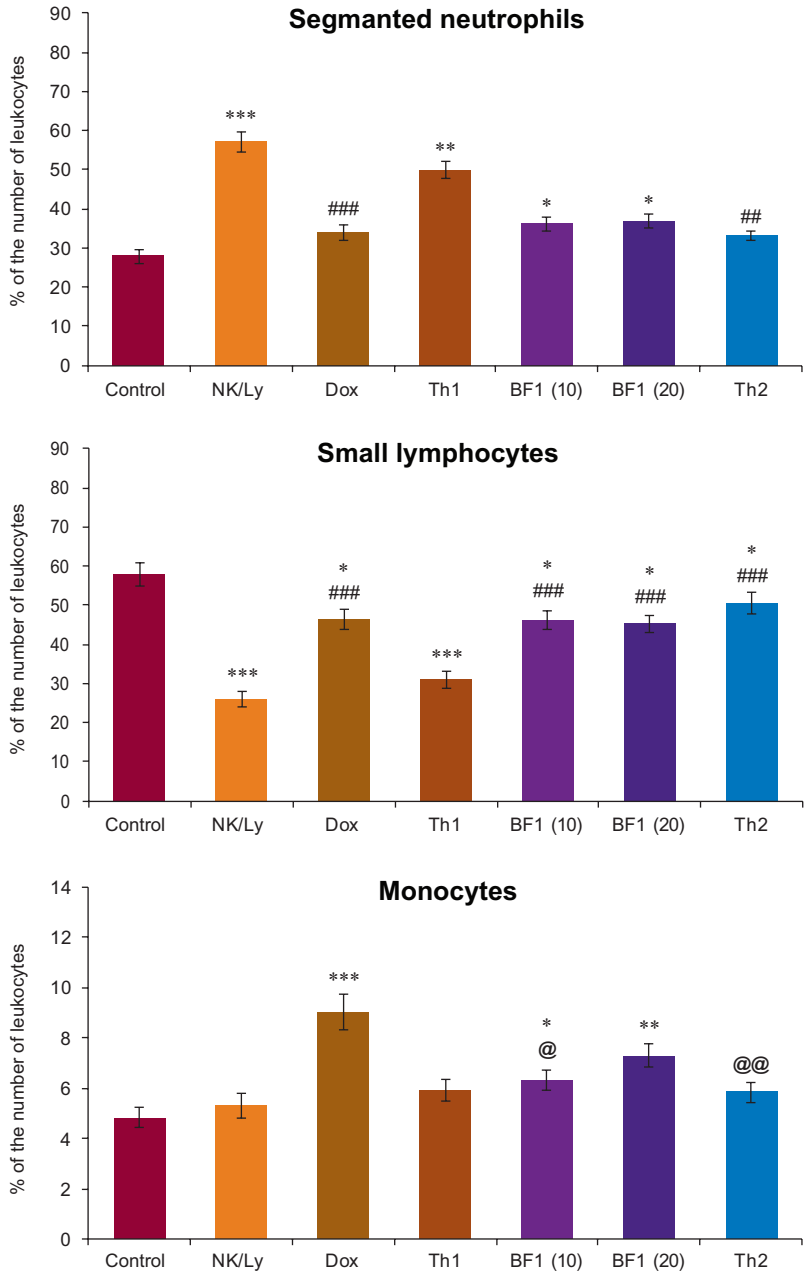

Fig. 3. Effect of thiazole derivative (BF1), unconjugated PEG-based polymeric nanoparticle (Th1) and complexes of BF1 with PEG-PN (Th2) on segmented neutrophils, small lymphocytes and monocytes in the blood of tumor-bearing mice. Mean ± SD; n = 5, * – P ≤0.05; ** – P ≤0.01; *** – P ≤0.001 compared to healthy control; # – P ≤0.05; ## – P ≤0.01; ### – P ≤0.001 compared to NK/Ly (untreated tumor-bearing mice); @ – P ≤0.05; @@ – P ≤0.01; @@@ – P ≤0.001 compared to Dox

significantly increased the number of small lymphocytes by 78.4 %, 77.1 %, 73.3 %, and 93.7 %, respectively, compared to untreated tumor-bearing animals (P ≤0.001).

The monocytes count has increased under the action of doxorubicin and BF1 in concentrations of 10 and 20 mg/kg in the blood of tumor-bearing mice by 86.2 %, 30.1 % and 50.6%, respectively, compared to intact animals (P ≤0.05, P ≤0.01, P ≤0.001). The Th2 complex did not induce monocytosis in NK/Ly lymphoma mice compared to controls and effectively normalized monocytes count compared to Dox.

The number of banded neutrophils increased in untreated mice with lymphoma, as well as under the action of unconjugated PEG-PN and BF1 at concentrations of 20 mg/kg by 47 %, 58 % and 29.9 %, respectively (P ≤0.05), compared to control values (3.3±0.3 %). Doxorubicin, BF1 at a concentration of 10 mg/kg and the Th2 complex did not affect the number of banded neutrophils in tumor-bearing mice compared to healthy animals.

The number of large lymphocytes did not change either in untreated tumor-bearing mice or in animals with lymphoma treated with the investigated compounds compared to intact mice.

The effects of doxorubicin (Dox), PEG-based polymeric nanoparticles (Th1), thiazole derivative (BF1) and thiazole derivative complex with polymer nanoparticles (Th2) on the number of erythrocytes, leukocytes and leukocyte blood formula of mice with NK/Ly lymphoma on the 14th day after tumor inoculation (M±SD)

Groups	Leucocytes ($\cdot 10^6$/мл)	Erythrocytes ($\cdot 10^9$/мл)	Segmented neutrophils (%)	Banded neutrophils (%)	Small lymphocytes (%)	Large lymphocytes (%)	Monocytes (%)
Control (healthy)	6.8±0.3	8.7±0.6	27.9±1.8	3.3±0.3	57.9±3.1	6.0±0.4	4.9±0.4
Control (NK/Ly)	12.3±1.2***	9.2±0.7	57.1±2.7***	4.9±0.4*	26.1±1.9***	6.6±0.5	5.3±0.5
Dox (1 mg/kg)	5.1±0.4**	6.3±0.3***	33.9±2.0###	3.6±0.3	46.5±2.6*###	7.0±0.4	9.0±0.7***
PEG-PN Th1 (20 mg/kg)	10.5±0.9***	8.0±0.5	49.8±2.1**	5.2±0.4*	31.0±2.1***	8.0±0.5	5.9±0.4
BF1 (10 mg/kg)	5.9±0.3###@	7.8±0.5###	36.1±1.7*	4.1±0.4	46.2±2.5*###	7.3±0.5	6.3±0.4*@
BF1 (20 mg/kg)	5.8±0.3###@	8.7±0.6*###	36.9±1.6*	4.3±0.4*	45.2±2.3*###	6.3±0.4	7.3±0.5**
Complex Th2 (10 mg/kg)	6.5±0.4###@@	8.5±0.5###	33.0±1.2##	4.0±0.3	50.5±2.7*###	6.6±0.4	5.8±0.4@@

Comments: Mean ± SD; n = 5; * – P ≤0.05; ** – P ≤0.01; *** – P ≤0.001 compared to healthy control; # – P ≤0.05; ## – P ≤0.01; ### – P ≤0.001 compared to NK/Ly (untreated tumor-bearing mice); @ – P ≤0.05; @@ – P ≤0.01; @@@ – P ≤0.001 compared to Dox

DISCUSSION

In the last few decades, the development of DDS has enabled the development of many pharmaceutical products into successful anticancer therapies. This delivery technology of chemotherapy agents substantially influenced bioavailability of medicine, improving the solubility of drugs, controlling their release, broadening their activity, and adjusting their pharmacokinetics (Ahmed, Rehman & Tabish, 2022; Cheng *et al.*, 2021;

Gavas, Quazi & Karpiński, 2021). However, in recent years, many studies showed specific organ toxicity of these substances, especially of the liver, heart and blood.

Hepatotoxicity is a common clinical indicator that is associated with a range of anticancer therapies including chemotherapy (Mudd & Guddati, 2021). Besides, many nanomaterials have been described to accumulate in the liver and induce liver injury (Vilas-Boas & Vinken, 2021). The induction of oxidative stress that affects the prooxidant-antioxidant balance is the manifestation of toxicity most frequently reported following exposure of cells or animal models to different therapeutic drugs and nanomaterials (Vilas-Boas & Vinken, 2021).

It was found that thiazole derivative BF1 did not cause oxidative stress and did not influence the amount of primary and secondary LPO products (hydroperoxides and TBA-positive products, respectively) in BF1-treated murine hepatocytes. The change in the amount of LPO products was not recorded under the influence of either unconjugated PEG-PN Th1 or its complex with BF1 – Th2 in hepatocytes of mice with grafted NK/Ly.

However, an altered oxidative status and decreased oxidative defenses can also be observed as GPx, SOD, and CAT levels decrease (Bostan *et al.*, 2016). It was reported that neither BF1, PEG-PN nor their complex Th2 changed the level of AOS enzymes in hepatocytes cell lines from mice with NK/Ly.

This data may indicate the absence of significant hepatotoxicity in the application of complex BF1+PEG-PN with a more pronounced therapeutic effect compared to unconjugated BF1.

Nanoparticles and their complexes with therapeutic agents can interact with the hematopoietic system that is responsible for leukocyte and erythrocyte production and with the mononuclear phagocyte system. The DDS approach requires the nanodrugs to have a long half-life, which can be difficult to achieve because they are mostly rapidly eliminated through complement activation and phagocytes.

The coating of nanocarriers with hydrophilic polymers, such as PEG, can increase the blood circulation time of nanodrugs (van Leent *et al.*, 2022). However, it can provoke or enhance the side effects of these agents on the hematopoietic system and circulating blood cells. Hemocompatibility testing is one of the main steps in the evaluation of interactions between DDS and the different components of blood to determine if any side effects may arise from the exposure of these foreign materials to blood (de la Harpe *et al.*, 2019). One of the effective ways to study the safety of a drug is an estimation of the number of red and white cells, and their percentage ratio.

Progression of NK/Ly lymphoma in mice led to leukocytosis and caused an increase in the number of lymphocytes. It is known that an increase in the total number of leukocytes in the blood is a characteristic sign of the inflammatory process caused by tumor growth (Chmielewski & Strzelec, 2018). The antitumor drug Dox significantly reduced the number of leukocytes and caused leukopenia in NK/Ly mice. The investigated compound BF1 and its complex normalized the number of lymphocytes and did not cause leukopenia, as was the case during treatment with Dox.

Under the action of doxorubicin and BF1, the growth of monocytes in the blood of tumor-bearing mice was recorded. An increased number of monocytes is an immune reaction of the body in numerous pathologies. In addition, monocytosis under the action of some antitumor drugs is explained by their powerful proapoptotic effect, resulting in the formation of a large number of apoptotic bodies. Considering the fact that monocytes are the precursors of macrophages, whose function is, in particular, to phagocytize

apoptotic bodies, the growth of monocytes in the blood of mature animals under the action of antitumor compounds can be considered a normal reaction of the body (Kiss *et. al.*, 2020). The Th2 complex did not induce monocytosis in NK/Ly lymphoma mice compared to controls and effectively normalized monocyte count compared to Dox.

The major limitations of the study were: 1) the lack of data on the dosages and the trough levels of thiazole derivative BF1 and PEG-PN Th1 were not captured; 2) small sample size (5 mice/group) and the absence of a longer follow up so that no conclusion can be drawn about long term treatment. In future, experiments must be conducted with a view to generalising results with a longer follow up to assess the recurrence and long term reproductive outcome.

Thus, thiazole derivative BF1 showed a weaker toxic effect than the known antitumor drug doxorubicin, and the number of erythrocytes in the blood of mice with NK/Ly lymphoma treated with BF1 and its complex with PEG-PN remained at the control level. The progression of lymphoma in mice led to an increase in the total number of leukocytes and segmented neutrophils in particular, however BF1 and its complex with the polymer carrier PEG-PN significantly reduced the number of these cells and showed an immunomodulatory and protective effect on the hematopoietic system of tumor-bearing animals. In addition, Th2 complex normalized the number of segmented neutrophils almost to the control level.

The data described above indicate that the investigated PEG-PN is not only safe for non-cancer cells but also improves the therapeutic effect of BF1.

CONCLUSION

Thiazole derivative BF1 in complex with PEG-based polymeric nanoparticle Th1 did not induce hepatotoxicity, had a less cytotoxic effect on blood hematological parameters compared to Dox, and showed an immunomodulatory and protective effect on the circulating blood cells in mice with grafted NK/Ly.

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 institutional, 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.N.B.]; project administration, [A.M.B.]; funding acquisition, [-].

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АНАЛІЗ ПРОФІЛЮ БЕЗПЕКИ ПОХІДНОГО ТІАЗОЛУ І ЙОГО КОМПЛЕКСУ З ПЕГ-ВМІСНИМИ ПОЛІМЕРНИМИ НАНОЧАСТИНКАМИ НА ПЕЧІНКУ ТА КЛІТИНИ КРОВІ МИШЕЙ-ПУХЛИНОНОСІЇВ

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Обґрунтування. Системи доставки ліків (СДЛ) продемонстрували вирішення багатьох проблем, пов'язаних з доставкою гідрофобних хіміотерапевтичних сполук до пухлинних тканин. Однак гепатотоксичність і пригнічення кровотворної системи є ключовими проблемами в клінічному лікуванні раку за допомогою СДЛ на основі наночастинок, що може обмежити їхнє медичне використання. Метою цієї роботи було дослідити дію похідного тіазолу N-(5-бензил-1,3-тіазол-2-іл)-3,5-диметил-1-бензофуран-2-карбоксаміду (BF1), кон'югованого з ПЕГ-вмісними полімерними наночастинками (PEG-PN – Th1) на гепатоцити та гематологічні параметри крові мишей із лімфомою NK/Ly.

Матеріали та Методи. Експерименти виконували на білих мишах самцях дикого типу з прищепленою лімфомою NK/Ly. Досліджувані сполуки BF1, PEG-PN Th1 та комплекс PEG-PN + BF1 (Th2) у кінцевій концентрації 10 мкМ додавали до зразків печінки й інкубували впродовж 10 хв, після чого визначали вміст продуктів перекисного окислення ліпідів й активність ферментів системи антиоксидантного захисту (АОС) відповідно до методів, описаних нижче. Окрім того, досліджували цитологічні показники крові після лікування мишей BF1 у концентраціях 10 і 20 мг/кг, ПЕГ-ПН (20 мг/кг) і Th2 комплексу (10 мг/кг). На 14-ту добу досліду в усіх груп відбирали зразки крові та підраховували кількість еритроцитів, лейкоцитів і лейкоцитарну формулу.

Результати. Встановлено, що ні BF1, ні PEG-PN, ні їхній комплекс Th2 не змінювали вміст продуктів перекисного окислення ліпідів і активність ферментів АОС у гепатоцитах мишей з NK/Ly. BF1 (у концентрації 10 мг/кг) і комплекс PEG-PN + BF1 не змінювали рівень еритроцитів миші порівняно з доксорубіцином. Усі досліджувані сполуки, крім PEG-PN, значно зменшували спричинений лімфомою лейкоцитоз і підвищували рівень малих лімфоцитів. Розвиток лімфоми NK/Ly призводив до збільшення кількості нейтрофілів, тоді як BF1 та його комплекс із PEG-PN значно зменшували його.

Висновки. BF1 і комплекс PEG-PN + BF1 мали обмежені негативні побічні ефекти у мишей з NK/Ly. Досліджувані сполуки не були гепатотоксичними щодо клітин печінки миші. Як BF1, так і його комплекс з PEG-PN не зумовлювали серйозних побічних ефектів на мишачі клітини крові.

Ключові слова: похідне тіазолу, полімерні наночастинки, система доставки ліків, гепатотоксичність, гематологічні показники

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