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COMPARISON OF CYTOTOXIC ACTIVITY OF CISPLATIN AND A CLUSTER RHENIUM (III) COMPOUND

We have shown that the cytotoxic activity of $Re_2Cl_2(C_3H_7CO_2)_4$ and cisplatin was close and the cytotoxic activity of the rhenium-platinum system was much more effective than that of $Re_2Cl_2(C_3H_7CO_2)_4$ and cisplatin. Liposomal formulations of investigated preparations are more effective than their solutions, due to a simplified transport mechanism and prevention of the deactivation before penetration to the cancer cell. The obtained results underline perspectives of the use of dirhenium compounds in medicines and emphasize the need of further investigations of mechanisms of anticancer activity of the cluster dirhenium (III) compounds.

Keywords: cluster rhenium compound; rhenium-platinum antitumor system; Jurkat cells; cytotoxic activity.

In our previous works it was shown that the cluster rhenium (III) compound dichlorotetra-μ-isobutiratodirhenium (III) $Re_2(i\text{-}C_3H_7COO)_4Cl_2$ – (**I**) exhibited pronounced anticancer and antiradical activities *in vivo*, especially effective in combination with cisplatin (Re-Pt system) [22]. Besides, in these and other experiments it was shown that **I** had antioxidant, hepato- and nephroprotective activity in the models of cancer growth and nephrotoxicity [2, 8, 10, 21]. To our mind the compound **I** has several structural features, which might be responsible for the above indicated properties: binuclear clustering of rhenium atoms as the main component of the molecule that is characterized by low toxicity; quadruple bond, which is responsible for antiradical and antioxidant properties; chlorine atoms, which are able to interact with polar molecules; branched alkyl groups and their symmetrical arrangement that provide hydrophobic interactions. **I** showed cytotoxicity against CEM-T4 cells and possibility to interact with supercoiled DNA [14]. Recently the dirhenium cluster compound with an amino acid ligands was tried against T-cells of acute lymphoblastic leukemia (Jurkat cells) [15] and it was shown that it had close to cisplatin toxicity but more proapoptotic than pronecrotic cisplatin action. One of the directions of further studies of the compound **I** and other cluster rhenium compounds is to find

the optimal modes of administration of **I** alone or in the Re-Pt system, in which an effective anticancer activity can be achieved. Also, further investigation of influence of new dirhenium (III) compounds and rhenium-platinum antitumor systems on the human cancer cells is of great importance.

Thus, the aim of this work was to study the influence of **I** and cisplatin in solution and in liposomal forms against T-cells of acute lymphoblastic leukemia (Jurkat cells) and to find difference and synergism in these interactions.

Materials and Methods

Cisplatin and dichlorotetra-μ-isobutyratodirhenium (III) $Re_2(i\text{-}C_3H_7COO)_4Cl_2$ (**I**) were synthesized at Ukrainian State University of Chemical Technology at the Department of Inorganic Chemistry [5, 21]. Liposomes were prepared according to a published procedure [11]. The Jurkat cells were obtained from the Institute of Cell Biology National Academy of Sciences of Ukraine (Lviv).

The following treatment variants were assessed: solution of cisplatin cPt - cPt; solution of **I - I**; **I** in liposomal form - [**I**]; cPt in liposomal form – [cPt]; The final concentrations of the administered rhenium substance were 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8} and 10^{-9} M. The rhenium-platinum system was administered in two ways: free **I** and cisplatin in molar ratio 4:1- **I** + cPt; **I** in liposome form plus cisplatin in a molar ratio 4:1 – [**I**] + cPt so that the concentration of cisplatin was 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8} and 10^{-9} M.

Jurkat cells were cultured in 20 cm^2 Carrel glass culture flasks in medium RPMI 1640 (Sigma, USA) with addition of 10% bovine serum (Sigma, USA). The cells were passaged every two days at the concentration 5 x 10^5 cells/ml of culture medium. The cells were plated in 24-well plastic plates (Sarsted, USA) at the concentration 5 x 10^5 cells/ml. The studied compounds were added at various concentrations noted above. After 24, 48, 72, 96 hours of incubation, the alive and dead apoptotic cells were counted according to [9, 14]. In detail: To evaluate the viability of cells, 10 μl of 1% trypan blue (Sigma, USA) solution was added to 100 μl of suspension and incubated for 2-3 min. 20 μl of coloured suspension of cells was added to a Goryaev's chamber and dead and living cells were counted with a luminescent microscope LOMO Mikmed-2 variant 12 (St. Petersburg, Russia) an increase by 200 times. Under these conditions, the living cells differed from the non-viable (dead) ones by the inability to absorb the dye [14]. LC_{50} index was used, calculated as a lethal concentration of drug, which kills 50 % cells in comparison with a control culture by Reed–Muench method [17].

Statistical analysis of the obtained data was carried using the Student's t-test ($p \leq 0.05$). The data were expressed as $M \pm m$.

Results and discussion

The dependence of viability of the cells on the concentration of **I,** cisplatin (cPt) and the rhenium-platinum system in solutions forms is shown in Figure 1.

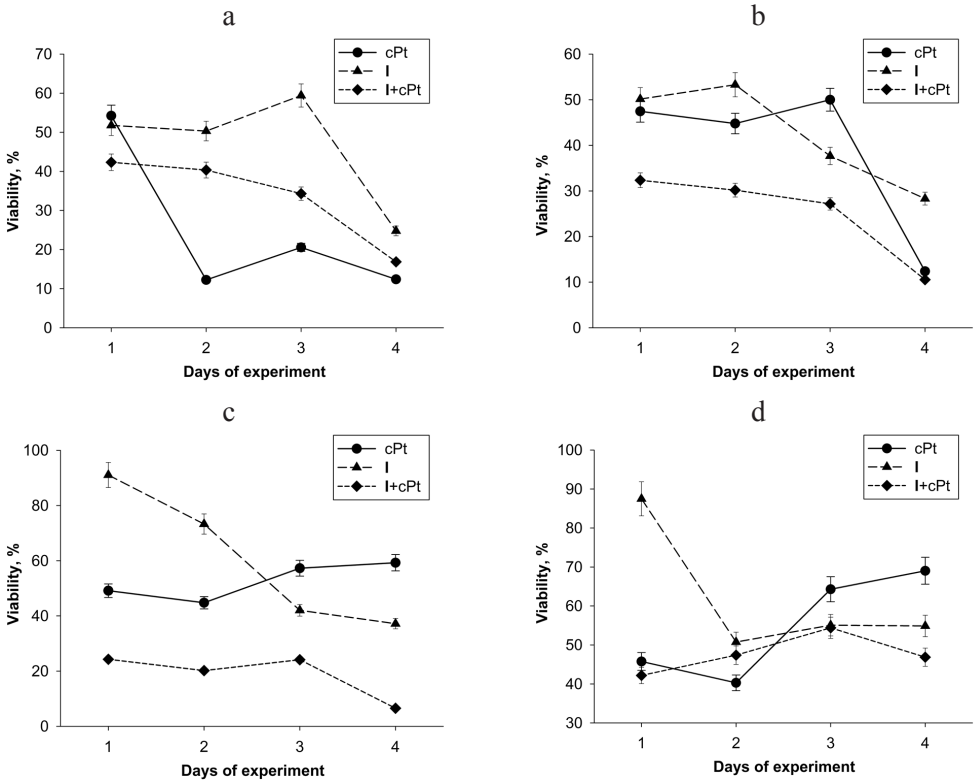

*Fig. 1. Cytotoxicity of cPt, **I** and cPt + **I** in free forms in concentrations: a – 10^{-5}, b – 10^{-6}, c – 10^{-7}, d – 10^{-8} M*

As it is clear, the cytotoxic activity of **I** and cisplatin was close and the cytotoxic activity of the rhenium-platinum system was much more effective than that of **I** and cisplatin. There was no linear concentration dependence in obtained results for I and cisplatin in these experiments that may be explained by non-monotonic development of the Jurkat cells population, Fig. 2.

As the most intensive growth and quantity of the cells are found on the 4th day, it is reasonable to compare the results on the 4th day: under high concentration 10^{-5}M of components the cytotoxic activity of the introductions has the following range cisPt > cisPt + **I** > **I;** under concentration 10^{-6}M cPt + **I** = cPt > **I** and under the 10^{-7}M and lower it becomes cisPt + **I** > **I** > cisPt, absolutely vice versa. It means, that in the range of low concentrations **I** is more effective in solutions than cisplatin and that both cytostatics had synergistic or additive effect. This may be the explanation of much lower toxicity of the rhenium compounds in our experiments with Guerink carcinoma and partly the efficacy of the dirhenium (III) based therapy. As for the rhenium-platinum system on its base, it is not possible to compare as the concentration of **I** in these experiments is four times higher and was introduced following the

experiments *in vivo*, where the rhenium-platinum antitumor system was introduced in the ratio 1 : 4 (cisplatin : a rhenium substance).

Introductions of the liposomes also led to death of Jurkat cells during all days of the experiment, Fig.3.

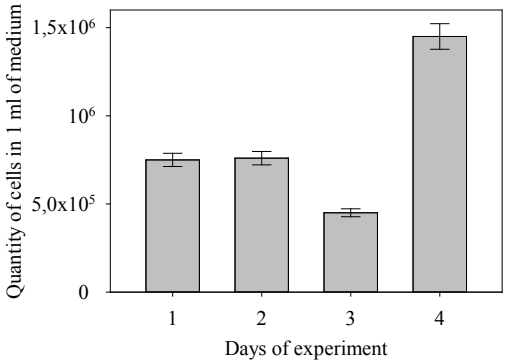

Fig. 2. Growth of Jurkat cells in control

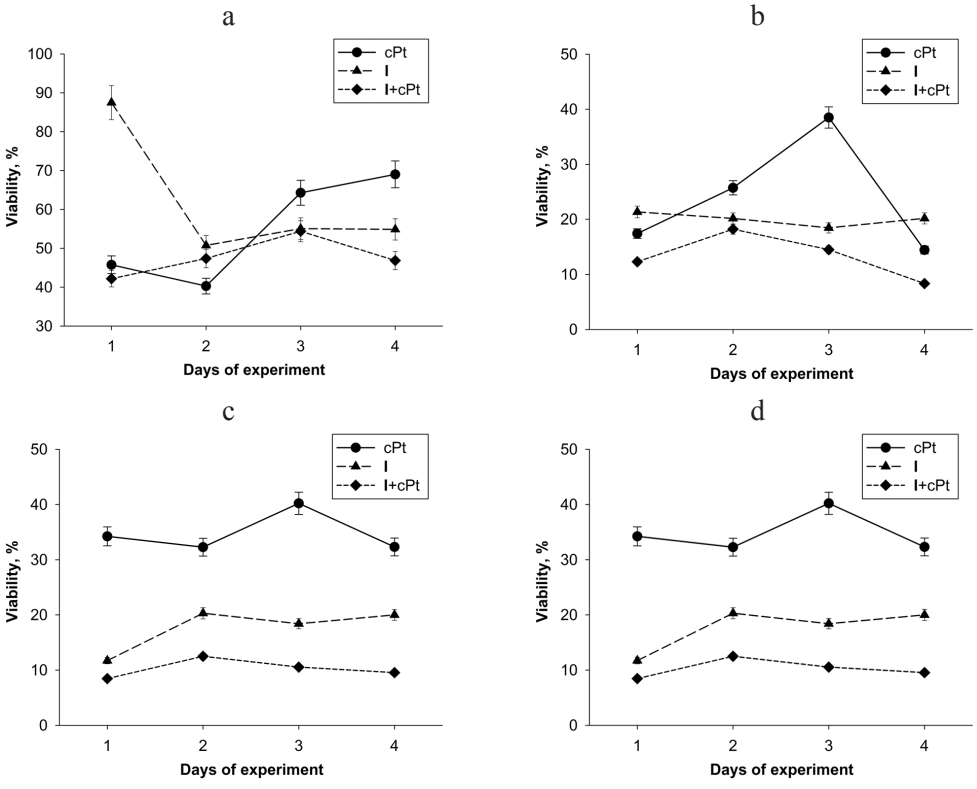

*Fig. 3. Cytotoxicity of [cPt], [**I**] and cPt + [**I**] in liposomal forms in concentrations: a – 10^{-5}, b – 10^{-6}, c – 10^{-7}, d – 10^{-8} M*

According to the presented data, it is obvious, that liposomal formulations of all investigated preparations are more effective in these experiments than their solutions, that is not a surprise as the lipid encapsulation of rhenium compounds and cisplatin increased the concentration of these cytostatics in the cancer cell through a simplified transport mechanism and prevented the possibility to deactivate these compounds in the culture environment that leads to increasing of the compounds' reactivity [3, 24]. It is interesting that lowering of concentration of preparations decreased the efficacy only of cisplatin, neither of **I** nor of the system on its base. Unfortunately, it is very difficult to interpret such data as the mechanism of anticancer activity of the dirhenium (III) compounds is not fully investigated.

I had cytotoxic activity close to cisplatin in solution but had more cytotoxic activity in liposomal form; also, we have shown the significant advantage of cytotoxic activity of the system in liposomal forms as compared to cisplatin, Fig. 4.

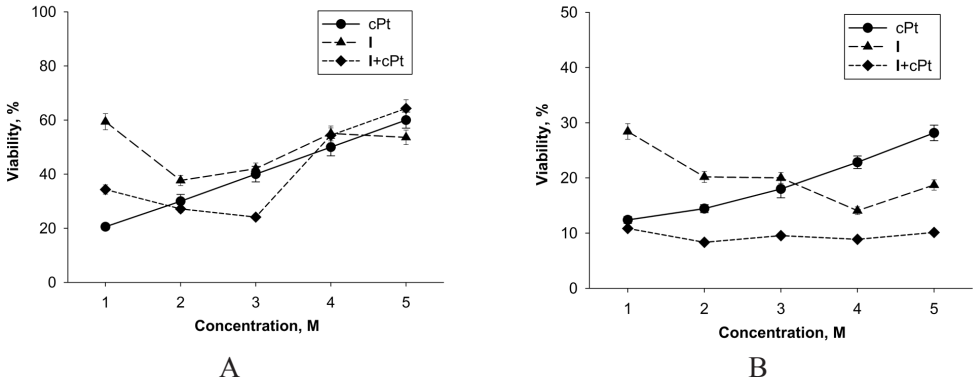

Fig. 4. Viability of Jurkat cells under changing of concentrations of components ($1 – 10^{-5}$, $2 – 10^{-6}$, $3 – 10^{-7}$, $4 – 10^{-8}$, $5 – 10^{-9}$ M) on the 4th day of experiments: A – introduction of components in solution; B – introduction of components in liposomes

LC_{50} for free cisplatin on this cell line was calculated and was $1.92 \cdot 10^{-6}$ M [16], the same value can be obtained for cisplatin from our data presented in Fig. 4 A. It is difficult to calculate LC_{50} for other substances in our investigation because they do not have linear concentration dependences, especially the system, but from the data in Fig. 4 we may conclude that [**I**] and [**I** + cPt] have LC_{50} in the range of 10^{-8} M, which is comparable with the LC_{50} values for the known antitumor drugs obtained on the same cell line, such as taxol (Paclitaxel [12], doxorubicin, newly synthesized heterocyclic 4-thiazolines, landomycin A, adriamycin [9] and palladium complexes with organic ligands [1].

The absence of linear dependence of cytotoxic activity on concentration may be explained by the fact that dirhenium(III) compounds were characterized by hydrolysis in aqueous solutions, the speed of which depended on the pH and on the structure of the complex [6].

Cisplatin is a prooxidant and cluster rhenium compounds are powerful antioxidants, which was shown in numerous works [18-20, 22]. Chemotherapy of redox modulation, aimed at changing the level of reactive oxygen species (ROS) in cancer cells is considered a promising strategy in cancer care. So, the prooxidants, increasing ROS level in cancer cell, led to its death. But some antioxidants were shown to exhibit cytotoxic effects, such as umbeliprenin (terpenoid coumarin, π-conjugated antioxidant) caused apoptotic death of Jurkat cells (LC_{50}=25μM), even in the presence of interleukin [22], which initiated resistance to apoptotic death of leukaemic cells [26]. Some antioxidants such as sodium selenite, selenomethionine, D-pantetine were tried in several Jurkat cells [9, 14], but they even reduced the toxicity of doxorubicin. The anticancer effect of such antioxidants as curcuminoids is well-known [13, 25]. It was explained by inhibition of NF-κB pathway by reducing ROS concentrations that were shown to be signaling molecules for NF-κB pathway and directly inhibited immune competent cells (ICC) - kinase activity by modifying cysteine residues critical for functioning of cancer cells [4, 7]. As signalling pathways of cancer cells that are influenced by cluster rhenium compounds have not been studied; as some of these compounds interact with DNA and histidine residues of proteins depending on the structure and orientation of the ligands around the cluster fragment, i.e., additionally have diverse coordination functions [22], in our opinion, the anticancer effect of these compounds depends not only on their antioxidant properties, but also on their possibility to influence other regulatory processes of cancer cell.

Conclusions

1. We have shown that the cytotoxic activity of **I** and cisplatin was close and the cytotoxic activity of the rhenium-platinum system was much more effective than that of **I** and cisplatin.

2. In the range of low concentrations **I** is more effective in solutions than cisplatin that may be the explanation of much lower toxicity of the rhenium compounds and their efficacy in experiments *in vivo*.

3. Liposomal formulations of the investigated preparations are more effective than their solutions, due to a simplified transport mechanism and prevention of the deactivation before penetration into the cancer cell.

4. Liposomal **I** and antitumor system on its base have LC_{50} in the range of 10^{-8} M, that is comparable with the LC_{50} values for the known antitumor drugs and underlines the importance of further investigations of the rhenium cluster compounds as anticancer species.

5. The obtained results emphasize perspectives of the use of dirhenium compounds in medicines and the need of further investigations of mechanisms of anticancer activity of the cluster dirhenium (III) compounds.

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ПОРІВНЯННЯ ЦИТОТОКСИЧНОЇ АКТИВНОСТІ ЦИСПЛАТИНУ ТА КЛАСТЕРНОЇ СПОЛУКИ РЕНІЮ (III)

Резюме

У зв'язку з попередніми даними про протипухлинну активність кластерних сполук ренію (III) і їх синергізм з цисплатином великий інтерес представляють порівняльні дослідження впливу цих сполук з цисплатином на лейкозні клітини людини. Мета роботи - порівняти цитотоксичну активність кластерної сполуки ренію $Re_2Cl_2(C_3H_7CO_2)_4$ (**I**) у розчинах і наноліпосомах окремо і разом з цисплатином у клітинах Jurkat. Цитотоксичність цих речовин досліджували щодо Т-клітин гострого лімфобластного лейкозу (клітин Jurkat) загальноприйнятими методами. Показано, що цитотоксична активність **I** і цисплатину має близькі значення, а цитотоксична активність системи реній-платина була значно ефективнішою, ніж у **I** та цисплатину. У діапазоні низьких концентрацій **I** більш ефективний у розчинах, ніж цисплатин, що може бути поясненням значно меншої токсичності сполук ренію та їх ефективності в експериментах *in vivo*. Ліпосомальні форми досліджених препаратів більш ефективні, ніж їх розчини, завдяки спрощеному транспортному механізму і запобіганню дезактивації перед проникненням у ракову клітину. Ліпосомальна форма **I** і протипухлинна система на її основі мають LC50 у діапазоні 10^{-8} М, що можна порівняти зі значеннями LC50 для відомих протипухлинних препаратів і підкреслює важливість подальших досліджень кластерних сполук ренію як протипухлинних речовин. Отримані результати підкреслюють перспективність використання сполук ренію (III) у медицині і необхідність подальших досліджень механізмів протипухлинної активності кластерних сполук ренію (III).

Ключові слова: кластерна сполука ренію; реній-платинова протипухлинна система; цитотоксична активність; апоптоз.

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