Iran J Public Health, Vol. 52, No.8, Aug 2023, pp.1776-1778

Letter to the Editor

Health Benefits of Modificated Multiplatinum Derivatives as Strategies for Overcoming the Cisplatin Resistance

Stefka Achkova Ivanova [1], *Danka Petrova Obreshkova [1], Lili Plamenova Peikova [2]

1. *Department of Pharmaceutical Chemistry and Pharmacognosy, Faculty of Pharmacy, Medical University-Pleven, Pleven 5800, Bulgaria*
2. *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Medical University-Sofia, Sofia 1000, Bulgaria*

***Corresponding Author:** Email: phddanka@yahoo.com

(Received 10 Jul 2022; accepted 15 Jul 2022)

Dear Editor-in-Chief

New strategies for the development of platinum anticancer drugs and for bypassing of resistance to Cisplatin derivatives and their toxicity are developed (1):

1) Trans-Pt II complexes
2) Mononuclear Pt II compounds with non-covalent binding to DNA by dipole-dipole interactions
3) Mononuclear monofunctional Pt II complexes
4) Chiral Pt II complexes
5) Polynuclear platinum agents with non-covalent binding to DNA by H-binding interactions
6) Pt IV prodrugs, releasing classical Pt II anticancer agents
7) Platinum complexes with targeted action.

Polynuclear (2) platinum complexes form DNA adducts through 1,4-strands and the resistance is overcome by inhibition of the reparative synthesis of damaged DNA (Fig. 1).

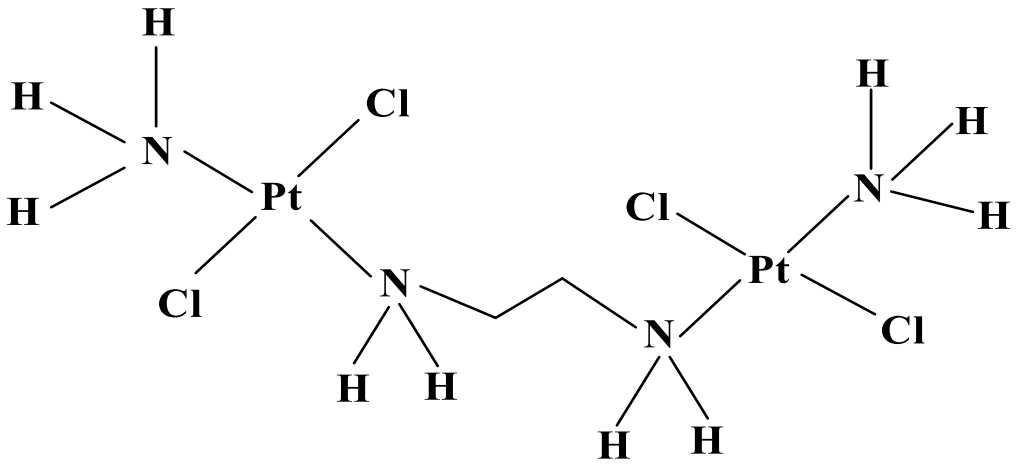

Fig. 1: Chemical structure of dinuclear platinum complex

A tri-core platinum complex BBR3464 (Fig. 2) is with a high ability to interact with DNA and exhibits antitumor activity in colorectal cancer at lower concentrations than Cisplatin; without nephron- and neurotoxic effects (2).

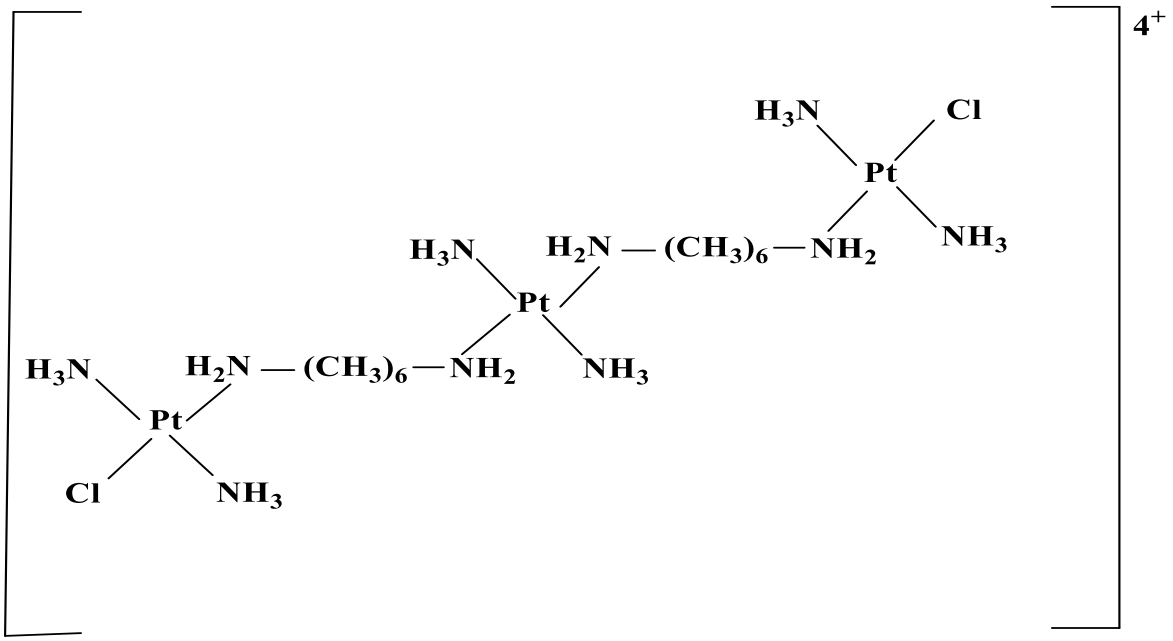

Fig. 2: Chemical structure of trinuclear platinum complex BBR3464

One of the strategies for reduction of toxicity and resistance is the use of "prodrugs", which can be activated locally. Activation of Pt IV complexes oral drug Satraplatin is accomplished by reduction to Pt II complexes, which is a necessary for achieving higher antitumor activity (3).
The new approaches in the development of new platinum antineoplastic complexes are fixed in increasing of antitumor activity, creation of cytostatic with targeted action, and decreasing the toxicity. The tendencies for creation of platinum complexes with targeted action are (4):
1) Anti metastatic complexes of Pt II with bisphosphonates with pronounced affinity for bone tissue
2) Hepatotropic antitumor complexes of Pt II, accumulating in the liver, through the expression of specific transport proteins on the membranes of hepatocytes: Bamet-R2 (cis-diaminodichlorocholylglycinate Pt II), without side effects typical of Cisplatin and analogs.
3) Estradiol and Testosterone ligands with high affinity for receptors expressed in cancers
Another important trend for creation of platinum complexes with targeted action is development of chemotherapeutic nanocarriers for delivery of platinum anticancer drugs (5) as polymers (6), and liposomes (7). The binding of platinum cytostatic to polymers is an approach to ensure targeted release and cytotoxic action. Platinum conjugates with proteins (albumin), peptides, and aminoacids have been reported. "Nanocarriers provide enhanced delivery of platinum anticancer drugs, reduced drug influx, improved intracellular penetration, and increased concentration of platinum drugs in cancer cells." Development of new nanotechnological drug systems for targeted delivery of cytotoxic drugs and selective accumulation in tumor tissue, leads to increased cytotoxicity, enhancement of therapeutic efficacy, overcoming the drug resistance and reduction of the toxicity of the anticancer agents (5). Nanocarriers are:

1) Cyclodextrin capped gold nanoparticles as a delivery vehicle for a prodrug of Cisplatin.
2) Polysilsesquioxane nanoparticles for triggered release of Cisplatin.
3) Silk fibroin nanoparticles for controlled release of Cisplatin.
4) Nanoparticle formulations of Cisplatin.
5) Cisplatin-incorporated polymeric micelles.
6) Liposomal encapsulated Cisplatin (8) or Oxaliplatin (9).
Lipoplatin is a liposomal encapsulated Cisplatin for reduction of the systemic toxicity and for improvement of targeting to primary tumors and metastases. The encapsulation technology reduces side effects, minimizes toxic exposure to normal tissues, maximizes drug accumulation up to 200-fold greater into tumors compared to normal tissues. Lipoplatin has been applied in breast, head, neck, pancreatic and non-small cell lung cancer. Aroplatin is a lipophilic analog, cytotoxic to Cisplatin-resistant ovarian, and colorectal cancer, peritoneal carcinoma or sarcoma, malignant pleural mesothelioma, with not observed nephrotoxicity and myelosuppression (8).
Lipoxal is a liposomal encapsulated Oxaliplatin and has been studied in colorectal, gastric, pancreatic and non-small cell lung cancer with not observed hepato-, nephro- and cardiotoxicity, but with side effects as neuroto xicity, myelotoxicity, and neutropenia (9). Pro Lindac is a nanopolymer for the sustained Oxaliplati release against breast, lung and prostate cancer, with not observed neurotoxicity or neutropenia, but with limiting renal failure (10).

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Bai L, Gao C, Liu Q, et al (2017). Research progress in modern structure of platinum complexes. *Eur J Med Chem,* 140(1): 349–82.
2. Wang K, Gao E (2014). Recent advances in multinuclear complexes as potential anticancer and DNA binding agents. *Anti-Cancer Agents Med Chem*, 14(1):147–69.
3. Gibson D (2016). Platinum (IV) anticancer prodrugs – hypotheses and facts. *Dalton Trans,* 45(33): 12983–91.
4. Baudino TA (2015). Targeted cancer therapy: the next generation of cancer treatment. *Curr Drug Discov Technol*, 12(1): 3–20.
5. Patra JK, Das G, Fraceto, LF, et al (2018). Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol*, 16(1):1–33.
6. Xiao H, Yan L, Dempsey EM, et al (2018). Recent progress in polymer-based platinum drug delivery systems. *Progress Polymer Sci*, 87(1):70–106.
7. Zalba S, Garrido MJ (2013). Liposomes, a promising strategy for clinical application of platinum derivatives. *Expert Opin Drug Deliv,*10(6):829–44.
8. Koukourakis MI, Giatromanolak A, Pitiakoudis M, et al (2010). Concurrent liposomal Cisplatin (Lipoplatin), 5-Fluorouracil and radiotherapy for the treatment of locally advanced gastric cancer: a phase I/II study. *Int J Radiat Oncol Biol Phys*, 78(1): 150–55.
9. Stathopoulos GP, Boulikas T, Kourvetaris A, Stathopoulos I (2006). Liposomal Oxaliplatin in the treatment of advanced cancer: a phase I study. *Anticancer Res,* 26(2B): 1489–93.
10. Nowotnik DP, Cvitkovic E (2009). Prolindac™ (AP5346): a review of the development of an HPMA DACH platinum polymer terapeutic. *Adv Drug Deliv Rev*, 61(13): 1214–19.