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Replacement of Pt-based anticancer drugs by Ru-analogues - a mini-review

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Abstract
Platinum complexes are very important to their biological activities, especially in cancer treatment, targeting to induce tumor cell death. Cis-platin and its analogues were used in cancer chemotherapy maintaining various pathways. But when these Pt-based anticancer drugs were failed to reach their maximum expectation then researchers were eager to find new analogues so that it can cover all the deficiencies shown by them. In this review, by the survey of lot of papers I wish to reach how Ru-analogues had been introduced as alternatives.
Keywords: *Anticancer drugs, Cis-platin, Ruthenium analogues*

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I. INTRODUCTION

Cancer, often called malignancy, is a global problem which people get panic most. About 13-15% people of the world died by cancer. Rate is increasing due to the change of mass life style. Cancer can be defined as the uncontrolled cell division. Actually P-53 apoptosis gene is responsible for this cell division. In cancer cell this gene was damaged and control over the cell division vanishes. More than 100 types of cancer are available e. g., breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer, lymphoma etc. Depending on the type of variety, symptoms may vary. The treatment of cancer may include chemotherapy, radiation, and/or surgery. After the unexpected discovery of cisplatin[1], the most successful platinum based anticancer compound, attention to other anticancer metal-based drugs has been converted [2 – 7] in a search for less toxic and more effective drugs. Among all the platinum group metals used in the synthesis of effective anticancer drugs, a wide range of ruthenium compounds has been described, some of them with outstanding anticancer activity [8 – 15] and two of them, *i.e.* NAMI- A and KP1019, are currently involved in clinical trials [16 – 18].

Platinum analogues

In cancer therapy, Platinum-based drugs have become a main role; almost half of all cancer patients undergoing chemotherapeutic treatment are advised to take platinum drug [19]. In 1960s, Barnett Rosenberg discovered the antineoplastic activity of cis-platin and then its use in cancer therapy was known to all [20]. Actually the journey of cis-platin started not in 1960s, but in 1844, when it was first designed by Italian chemist Michele Peyrone [21]. It was known as Peyrone's chloride for a long time. But when Barnett Rosenberg, a biophysical chemist, accidentally discovered its utility as anticancer agent, the miracle had come out [22]. At that time, Rosenberg was trying to find the effect electric fields on bacterial growth. During these experiments, he found bacteria grew 300 times to their normal size, a very uncommon result, when he used platinum electrodes to generate the electric fields. Though, to figure out the result it took a while, but in the end he discovered the platinum electrodes were digested in the test solution, producing cis-platin. He published his remarkable findings in the journal Nature[1] and after three years later, in another paper [20] he showed that cis-platin could cure tumours in mice. After the approval by the US Food and Drug Administration in 1978, cis-platin had been used as a drug in cancer treatment.

The discovery and effectiveness of Cis-platin opened a new window infront of inorganic chemists. Observing the successful preliminary information of the anticancer action of cis-platin, chemists began to synthesis a range of platinum complexes [23] with diverse ligands and testing their anticancer activity. After the discovery of cis-platin about 3000 Pt-based drugs were designed as cis-platin analogues, but among them only 30-40 were given permission. After that only 4 or 5 were finally passed. When the chemists were eager to find various complexes they observed some collective rules which must be followed by the Pt-complexes to show anticancer property. These indicate that the platinum complex must have the geometry with square-planar array, neutral in charge, will surround by two *cis* am(m)ine ligands, and two *cis* anionic ligands. The negatively charged ligands form bond(s) with central metal atom platinum not so strongly, otherwise activity would be decreased. On the other hand, if they form the bonds weakly, the complex will show high toxicity. However, the two two negatively charged ligands or am(m)ine ligands could be replaced respectively by a chelating

dicarboxylate or chelating diamine. By following these rules a large drug preparation programme was started based on controlled variation of ligands. After that, another two platinum analogues were synthesized, commonly known as carboplatin and oxaplatin and were given permition by the FDA for clinical use in the United States [24]. These compounds were thought to be functioned by a mechanism similar to that of cis-platin.

After the initial clinical trials of cis-platin, many researches were conducted to find the actual pathway by which mechanism this drug can show its anticancer property. In the Lippard et al. review paper, mechanistic pathways for this process was discussed [25]. There are mainly four mechanistic ways- (i) cellular uptake, (ii) aquation/activation, (iii) DNA platination, and (iv) cellular processing of Pt–DNA lesions, leading to apoptosis.

Chloride ligands replacement by aqua molecules occur when cis-platin has been introduced in the cell because chloride ion concentration is lower (approximately 3–20 mM)than the the extracellular fluid (≈100 mM) [26]. From the paper of Dabrowiak et al., it was proven that for carboplatin the aqua ligand substitution rate is much more slowler and for this reason it has been assumed that activation by carbonate is required to bind to DNA [27]. This mechanism, however, is not applicable with cis-platin [28]. The cellular objective of the three FDA-approved platinum drugs and many other platinum compounds that had been under investigation, is nuclear DNA. The inserted platinum complexes add to the N7 positions of guanosine and adenosine residues, the nucleophilic centers on purine bases of DNA. The two labile ligands on the platinum center allow cross-linking of nearby guanine bases. To a smaller extent, the platinum center can bind to guanine bases from different DNA strands to form interstrand cross-links. A considerable distortion in the DNA double helix is observed by the major intrastrand dGpG cross-link [29].

Demerits of platinum analogues

Though there were many clinical successes by platinum based drugs cis-platin, carboplatin, and oxaliplatin but they showed a number of adverse side-effects [30]. Among them nephrotoxicity, fatigue, emesis, alopecia, ototoxicity, peripheral neuropathy, and myelosuppression can be mentioned [31, 32]. Another serious limitation of current platinum-based therapies is that their efficiency is restricted for most of the malignancy diseases with the development of cell resistancy [33]. To change the mechanism which gives rise to cellular resistance and to reduce the other side effects, deviating from the traditional structure of platinum analogues need to investigate. The thought behind the supposition was the structural change may result in an altered mechanism of action and, consequently, a different spectrum of antimalignancy activity.

Several structural geometries have been emerged. Some of the more general categories include *trans* diam(m)ine complexes [34], polyplatinum compounds [35], photoactivatable azide complexes [36], intercalator-linked species [37], and monofunctional compounds [38]. From Hambley's review article it is believed to act primarily [Pt(II) complex] as prodrugs that release active Pt(II) species following their intracellular reduction [39]. Lippard et al. investigated that the cationic monofunctional platinum(II) complex, cis-diammine(pyridine)chloroplatinum(II), cis-$[Pt(NH_3)_2(py)Cl]^+$ or cDPCP, a coordination compound has a significant anticancer property [40]. From a X-ray crystallographic study it was known that cis-$[Pt(NH_3)_2(pyridine)Cl]^+$ cation, also called pyriplatin, having only a single labile chloride ligand. Due to the presence of only one labile ligand it can form a monofunctional adduct with DNA i.e., only a single bond is formed between the platinum centre and a donor atom on DNA and further it can be said that pyriplatin induced slight distortion of the DNA double helix upon binding in comparison to the structure of DNA bearing a cisplatin 1,2-intrastrand cross-link [41].

For decades, although cisplatin has been a crucial chemotherapy drug in treating patients with various types of cancer, drug resistance has been a major clinical barrier. Cis-platin shows its cytotoxic effects in tumar cells mainly through the formation of Pt-DNA adducts and subsequent DNA damaging. Ther are many clarifications of mechanism such as decreased drug accumulation, enhanced detoxification activity, promotion of DNA repair capacity, and inactivated cell death signaling. To reduce cis-platin resistance, combinatorial therapies were developed and have proven more effective to defeat cancers. Thus, understanding of the biochemical mechanisms triggered by cis-platin in tumor cells may lead to the design of more efficient platinum derivates (or other drugs) and might provide new therapeutic strategies and reduce side effects.

Introduction of Ruthenium

During the search of new non-platinum drugs with effective clinical importance, low toxicity and a broader spectrum of activity, rhodium and ruthenium were considered first. Non-platinum active compounds may be very effective in cancer therapy because they follow different mechanism of action. Ruthenium complexes are very special to overcome the registancy of cis-platin with low toxicity. Ruthenium, as we all know, shows many biochemical uses [42, 43].

Ruthenium analogues are used as immunosuppressant (cis-$[Ru(III)(NH_3)_4(HIm)_2]^{3+}$). When organic drugs coordinated to ruthenium centers ($[Ru(II)Cl_2(chloroquine)_2]$), it acts as antimicrobials against malaria and also for the treatment of Chaga´s disease. There are various examples of ruthenium analogues where they act as

antibiotics (ruthenium complexes of organicantibiotic compounds, e.g. the Ru(III) derivative of thiosemicarbazone against *Salmonella typhi* and *Enterobacteria faecalis*), nitrosyl delivery/scavenger tools (e.g. the Ru(III) polyaminocarboxylates known as AMD6245 and AMD1226 to treat stroke, septic shock, arthritis, epilepsyanddiabetes), vasodilator/vasoconstrictor agents and, as above mentioned, as drugs for cancer chemotherapy [8].

Dyson et al. showed that ruthenium(II) complex resembles in ligand-exchange kinetics to those of platinum(II) complexes which makes it the first choice in the search for compounds that display similar biological effects to platinum(II) drugs [8]. From this paper it was seen that how ligand exchange kinetics also play a vital role in biological activity. To show their desired therapeutic effect most of the drugs interact with macromolecules like proteins, or with small S-donor or even with water. Since the ligand exchange rate is fully dependent on the concentration of the exchanging ligands in the solution, diseases that alter these concentrations in cells or in the surrounding tissues may have an effect on the activity of the drug. In the platinum metal group only ruthenium has variable oxidation states (II-IV) which are accessible in the physiological pH. Among these three oxidation states the state III is someahat inert in physiological pH. In the body systems glutathione, ascorbate and single-electron-transfer proteins, like those involved in the mitochondrial electron-transfer chain, can reduce Ru(III) and Ru(IV) [44], always depending on the nature of the ligands, while molecular dioxygen and cytochrome oxidase can oxidize Ru(II) in certain complexes [45-47]. The redox potential of ruthenium compounds can be changed to improve the effectiveness of Ru-based drugs in the clinic [8].

Another interesting property of Ruthenium makes it very valuable in medicinal chemistry- ruthenium molecules is very selective towards biomolecules which is responsible for the low toxicity of ruthenium drugs [8]. There are two main proteins- transferrin and albumin used by mammals to solubilise and transport iron, thereby reducing its toxicity. From the literature survey it is proven that some ruthenium drugs can bind to transferring [48, 49]. As uncontrolled dividing cells, such as microbially infected or cancer cells needs more iron, they increase the number of transferrin receptors on their surfaces. This implies that the amount of ruthenium taken up by these infected or cancerous cells is greater than the amount taken up by healthy cells. This selective nature of the drug towards the diseased cells or cancer cells accounts for a reduction of its general toxicity.

II. CONCLUSION

There is no doubt about the grand success of cis-platin in medicinal chemistry as well as clinical field. Not only cis-platin but also some other platinum analogues are very much effective in the field of cancer treatment. The discovery of cis-platin showed a new pathway in chemical science research. Though some demerits were observed after some days but it had given new window to chemists. There were three pathway to recover its discrepancies-(1) Modification of Pt(II) Centre (2) Use of Co-medicines (3) Search for other metal complexes. My discussion was based on the last point where it was seen that Ruthenium can be used as an alternative option. Though there need more and more study but it can give some light.

REFERENCES

[1]. Rosenberg B., Van Camp L. and Krigas,T. (1965) Inhibition of Cell Division in *Escherichia coli*by Electrolysis Products from a Platinum Electrode. *Nature*, 205, 698–699.
[2]. Clarke M. J., Zhu F. C., Frasca D. R. (1999). Non-Platinum Chemotherapeutic Metallopharmaceuticals. *Chem Rev.* 99, 2511-2534.
[3]. Cleare M.J. (1974). Transition metal complexes in cancer chemotherapy. *Coord. Chem. Rev.*, 12, 349-405.
[4]. Köpf-Maier P. (1994). Complexes of Metals Other Than Platinum as Antitumour Agents. *Eur. J. Clin. Pharmacol.*, 47, 1-16.
[5]. Köpf-Maier P. and Kopf H. (1987). Non-platinum group metal antitumor agents. History, current status, and perspectives. *Chem. Rev.*, 87, 1137-1152.
[6]. Ott I. and Gust R. (2007). Non Platinum Metal Complexes as Anti- cancer Drugs. *Arch. Pharm.*, 340, 117-126.
[7]. Sadler P. J. (1991). Inorganic Chemistry and Drug Design. *Adv. Inorg. Chem.*, 36, 1-48.
[8]. Allardyce C. S. and Dyson P.J. (2001). Ruthenium in Medicine: Current Clinical Uses and Future Prospects. Platinum Metals Rev. 45, 62-69.
[9]. Ang W. H. and Dyson P. J. (2006) . Classical and Non- Classical Ruthenium- Based Anticancer Drugs: Towards Targeted Chemotherapy. *Eur. J. Inorg. Chem.*, 3993**.**
[10]. Clarke M. J. (2003). Ruthenium metallopharmaceuticals. *Coord. Chem. Rev.*, 236, 209-233.
[11]. Hotze A.C.G., Bacac M., Velders A.H., Jansen B.A.J., Kooijman H., Spek A.L., Haasnoot J.G. and Reedijk J. (2003). New Cytotoxic and Water-Soluble Bis(2-phenylazopyridine)ruthenium(II) Complexes. *J. Med. Chem.*, 46, 1743-1750.
[12]. Hotze A.C.G., Velders A.H., Ugozzoli F., Biagini-Cingi M., Manotti-Lanfredi A.M., Haasnoot J.G. and Reedijk J. (2000). Synthesis, characterization and crystal structure α-[Ru(azpy)2$(NO_3)_2$](azpy= 2-(phenylazo)pyridine) and the products of it reactions with guanine derivatives. *Inorg. Chem.*, 39, 3838-3844.
[13]. Ronconi L. and Sadler P.J. (2007). Using coordination chemistry to design new medicines. *Coord. Chem. Rev.*, 251, 1633-1648.
[14]. Yan Y.K., Melchart M., Habtemariam A. and Sadler P.J. (2005). Organometallic chemistry, biology and medicine: ruthenium arene anticancer complexes. *Chem. Commun.*, 4764-4776.
[15]. Zhang C.X. and Lippard S.J. (2003). New Metal Complexes as Potential Therapeutics. *Curr. Opin. Chem. Biol.*, 7, 481-490.
[16]. Hartinger C.G., Zorbas-Seifried S., Jakupec M.A., Kynast B., Zorbas H. and Keppler B.K. (2006). From Bench to Bedside--Preclinical and Early Clinical Development of the Anticancer Agent Indazolium trans-[tetrachlorobis(1H-indazole)ruthenate(III)] (KP1019 or FFC14A). *J. Inorg. Biochem.*, 100, 891-904.
[17]. Kostova I. (2006). Ruthenium Complexes as Anticancer Agents. *Curr. Med. Chem.*, 13, 1085-1107.

[18]. Rademaker-Lakhai J.M., van den Bongard D., Pluim D., Beijnen J.H. and Schellens J.H.M. (2004). A Phase I and Pharmacological Study With imidazolium-trans-DMSO-imidazole-tetrachlororuthenate, a Novel Ruthenium Anticancer Agent. *Clin. Cancer Res.*, 10, 3717-3727.

[19]. 19. Galanski M., Jakupec M. A. and Keppler B. K. (2005). Update of the preclinical situation of anticancer platinum complexes: Novel design strategies and innovative analytical approaches. *Curr Med Chem.* 12, 2075–2094.

[20]. Rosenberg B., Van Camp L., Trosko J. E. and Mansour V. H. (1969). Platinum compounds: A new class of potent antitumour agents. *Nature.* 222, 385–386.

[21]. George B. K. and Peyrone M. (2010), Discoverer of Cis-platin, *Platinum Metals Rev.*, 54, 250.

[22]. Bruce A. C. and Rosenberg B. In Memoriam (2010) *Cancer Res.* 70, 428-429.

[23]. Cleare M. J.and Hoeschele J. D. (1973) Studies on the antitumor activity of group VIII transition metal complexes. Part I. Platinum(II) complexes, *Bioinorg Chem.*, 2, 187–210.

[24]. Wheate N. J., Walker S., Craig G. E. and Oun R. (2010) . The status of platinum anticancer drugs in the clinic and in clinical trials, *Dalton Trans*., 39, 8113–8127.

[25]. Wang D. and Lippard S. J. (2005). Cellular processing of platinum anticancer drugs. *Nat Rev Drug Discov*, 4, 307–320.

[26]. Pil P. and Lippard S. J. (2002). Cis-platin and related drugs. In: Joseph RB, editor. *Encyclopedia of Cancer. New York: Academic Press*, 525–543.

[27]. Di Pasqua A. J., Goodisman J., Kerwood D. J., Toms B. B., Dubowy R. L. and Dabrowiak J. C. (2006). Activation of carboplatin by carbonate, *Chem Res Toxicol*, 19. 139–149.

[28]. Todd R. C., Lovejoy K. S. and Lippard S. J. (2007). Understanding the effect of carbonate ion on cis-platin binding to DNA, *J Am Chem Soc.*, 129, 6370–6371

[29]. Takahara P. M., Rosenzweig A. C., Frederick C. A. and Lippard S. J. (1995). Crystal-structure of double-stranded DNA containing the major adduct of the anticancer drug cis-platin. *Natur*e. 377, 649–652.

[30]. Von Hoff D. D., Schilsky R., Reichert C. M., Reddick R. L., Rozencweig M., Young R. C. and Muggia F. M. (1979). Toxic effects of *cis*-dichlorodiammineplatinum(II) in man. *Cancer Treat Rep*. 63, 1527–1531.

[31]. Coates A., Abraham S., Kaye S. B., Sowerbutts T., Frewin C., Fox R. M. and Tattersall M. H. (1983). On the receiving end – patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol. 19, 203–208.

[32]. Griffin A. M., Butow P. N., Coates A. S., Childs A. M., Ellis P. M., Dunn S. M. and Tattersall M. H. (1996). On the receiving end V: Patient perceptions of the side-effects of cancer chemotherapy in 1993. Ann Oncol. 7, 189–195.

[33]. Martin L. P , Hamilton T. C. and Schilder R. J. (2008). Platinum resistance: The role of DNA repair pathways. *Clin Cancer Res*. 14, 1291–1295.

[34]. Coluccia M, Natile G. *Trans*-platinum complexes in cancer therapy. Anticancer Agents Med Chem. 7(2007)111–123.

[35]. Wheate N. J. and Collins J. G. (2003) . Multi-nuclear platinum complexes as anticancer drugs. *Coordin Chem Rev*. 241, 133–145.

[36]. Bednarski P. J, Mackay F. S and Sadler P. J. (2007). Photoactivatable platinum complexes. *Anticancer Agents Med Chem.* 7, 75–93.

[37]. Baruah H., Barry C. G. and Bierbach U. (2004).Platinum-intercalator conjugates: From DNA-targeted cis-platin derivatives to adenine binding complexes as potential modulators of gene regulation. *Curr Top Med Chem.* 4, 1537–1549.

[38]. Johnstone T. C., Wilson J. J. and Lippard S. J. (2013). Monofunctional and higher-valent platinum anticancer agents. *Inorg Chem.* doi: 10.1021/ic400538c.

[39]. Hall M. D. and Hambley T. W. (2002). Platinum(IV) antitumour compounds: Their bioinorganic chemistry. *Coordin Chem Rev*. 232, 49–67.

[40]. Lovejoy K. S., Todd R. C., Zhang S., McCormick M. S., D'Aquino J. A., Reardon J. T., Sancar A., Giacomini K. M. and Lippard S. J. (2008). *Cis*-diammine(pyridine)chloroplatinum(II), a monofunctional platinum(II) antitumor agent: Uptake, structure, function, and prospects. Proc Natl Acad Sci USA. 105, 8902–8907.

[41]. Todd R. C. and Lippard S. J. (2009). X-ray crystal structure of a monofunctional platinum-DNA adduct, *cis*-$[Pt(NH_3)_2(pyridine)]^{2+}$ bound to deoxyguanosine in a dodecamer duplex. In: Bonetti A, Leone R, Muggia FM, Howell SB, editors. *Platinum and Other Heavy Metal Compounds in Cancer Chemotherapy. New York: Humana Press*. 67–72.

[42]. Zanzi I., Srivastava S. C., Meinken G. E., Robeson W., Mausner L. F, Fairchild R. G. and Margouleff D. (1989). A new cholescintigraphic agent: ruthenium-97-DISIDA. *Nucl Med Bio.* 16,397-403.

[43]. Srivastava S. C. (1996). Is there life after technetium: What is the potential for developing new broad-based radionuclides? *Semin Nucl Med*. 26, 119-131.

[44]. Clarke M. J., Bitler S., Rennert D., Buchbinder M. and Kelman A. D. (1980). Reduction and Subsequent Binding of Ruthenium Ions Catalyzed by Subcellular Components. *J Inorg Biochem*, 1279-87.

[45]. Stanbury D. M., Haas O. and Taube H. (1980). Reduction of oxygen by ruthenium(II) ammines. *Inorg Chem.* 19, 518-524.

[46]. Stanbury D. M., Mulac W. A., Sullivan J. C. and Taube H. (1980). Superoxide reactions with (isonicotinamide)pentaammineruthenium(II) and -(III). *Inorg Chem.* 19, 3735-3740.

[47]. Stanbury D. M., Gaswick D., Brown G. M. and Taube H. (1983). Autoxidation of binuclear ruthenium(II) ammines. *Inorg Chem.* 22, 1975-1982 .

[48]. Smith C. A., Sutherland-Smith A. J., Keppler B. K., Kratz F. and Baker E. N. (1996). Binding of ruthenium(III) anti-tumor drugs to human lactoferrin probed by high resolution X-ray crystallographic structure analyses. *J Biol Inorg Chem.* 1, 424 -431.

[49]. Hartinger C. G., Zorbas-Seifried S., Jakupec M. A., Kynast B., Zorbas H. and Keppler B. K. (2006). From bench to bedside – preclinical and early clinical development of the anticancer agent indazolium *trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)] (KP1019 or FFC14A). *J Inorg Biochem.* 100, 891-904.