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Research Article

Highly Promising an Anti-Cancer Drugs : Metal Complex Bearing Sulfur Chelating Ligand, A Hypothetical Design

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Abstract

In anticancer chemotherapy, drug targeting and delivery methods depend on agents with selective access to cancer cells to deliver drugs to the target, and approaches to finding such agents often depend on novel design strategies employing bioactive vectors. Platinum-based complexes are extremely important drugs for the treatment of cancer. Recently synthesized complexes of Pt (IV) have been shown to have several advantages, such as they are safer, can be used orally, are highly anti-cancer effective, there is no cross-resistance to cisplatin, and their effectiveness is compared with commonly used Pt (II) compounds such as cisplatin and oxaliplatin. A molecular mimicry model for the generation of new active drugs may be synthesized by the 3,5-ditert-butyl-2-hydroxy-benzylaminocysteine (DTHBAC) where a cysteine group and two tertiary butyl groups attached to the phenol aromatic ring can be coordinated with platinum. This appropriate ligand with the platinum complex is fit for the anticancer drug. Based on the present modeling, it can be recommended in the management of patients, and from this perspective, the status of the platinum anticancer drug field will develop over the next decade. Moreover, the authors have no doubt that this will benefit patients in the future and will be widely used in cancer treatment for years to come.

Keywords: Drug design, Anti-cancer, Cisplatin, Complex, Chelate.

Introduction:

Cancer is one of the leading causes of death in industrially developed countries. It is characterized by uncontrolled growth and the spread of abnormal cells in the body. Cancer is considered one of the most complicated diseases that humanity has ever faced. The complications of the treatment for this disease came from the great match between cancer and normal cells except for their highest rate of replication. Healthy tissue contains normal cells that constantly receive signals indicating whether the cell should divide, differentiate into another cell, or, on the contrary, push the cells to die in case of severe damage. Cancer cells developed autonomy from these replication signals, leading to uncontrolled growth and proliferation. This uncontrolled cell proliferation, if it is not stopped, will spread to other organs according to a process called metastasis that generally leads to a fatal issue[1]. Initiation and progression of cancer depend on environmental factors such as chemicals, radiation, and infectious agents, but also on internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These factors can act together or in sequence, resulting in abnormal cell behavior and excessive proliferation. However, these DNA mutations take months and years to accumulate before the tumor becomes clinically detectable[2]. Compounds that selectively modulate multiple targets can provide clinical benefits and are an alternative to traditional highly selective agents for unique targets. The discovery of a number of trans platinum complexes, including the in vitro and in vivo effectiveness of cisplatin as sensitive or resistant to tumor cells in the 1990s, led to a reassessment of platinum's efficacy as an antitumor drug. The determining factors for the cytotoxic efficacy of the trans-platinum complex do not follow the same pattern as cisplatin and its analogs. Therefore, new trans-plantin complexes can be designed by precisely identifying the differences in cellular biochemistry and pharmacology between the trans-platinum, and cisplatin antitumor complexes, and cisplatin might be methodically exploited to design new trans-platinum complexes with a clinical profile supplementary to that of cisplatin and related analogues[3]. Notwithstanding a tremendous strength of research and improvement in the field of metallopharmaceuticals, the platinum (II) complexes group continually leads in the number of patients treated as well as the number of drugs available on the market. The platinum (II) dichlorido complexes of general composition trans, which are the first complexes with N-donor ligands, support the idea that the investigated complexes could be used as pro-drugs[4]. Based on the concept of an existing novel molecular rationale for new platinum antitumor drug development, a pharmacophore-based drug design begins with a comparison of active and inactive compounds. This gives an idea of how structural variations can change the biological activity of a compound and allows the development of a hypothesis about the interactions between the molecule and its receptor. Metal

complexes, with their wide spectrum of coordination numbers, coordination geometries, thermodynamic and kinetic preferences for ligand atoms, and in some cases redox activity, offer novel mechanisms of action, which are unavailable to organic compounds[5]. This move is known as molecular impersonation and is based on the determination of the structural elements necessary for the activity of the lead complexes[6]. On the other hand, various barriers in the hypoxic solid tumor that has an important effect on drug transportation which impede anticancer efficacy[7] and enhances doxorubicin (DOX) chemotherapy by improving the transportation to cancer cells and inducing a neighboring effect with the assistance of monostearin (MS) coating, potentiating drug penetration into deep tumor tissues, designed a smart O_2 self-supplying nanocarrier. Petra et al[8] modified mannich reactions involving an ortho-quinone methide (o-QM) intermediate were classified on the basis of the o-QM source followed by the reactant, e.g. the dienophile partner in cycloaddition reactions (C=C or C=N dienophiles) or by the formation of multicomponent Mannich adducts. A laser flash photolysis was addressed by Rokita et al[9], showing the formation and reactivity of these intermediates strongly depended on the presence of electron-donating or electron-withdrawing functional groups of the o-QM precursors. A gallium complex of (R)-2-(5-chloro-2-hydroxybenzylamino) succinic acid (GS2) in combination with cytotoxic chemotherapy was proposed by Ahmed[10]. It is a promising compound for anti-invasive and anticancer therapy and may be a potential candidate to decrease the Matrix Metalloproteinases (MMP)-14 activity in cancer metastatic diseases presenting a high level of MMP-14 expression and activity. These results encourage us to proceed to in vivo evaluation of the antitumor activity of GS2 over the tumor-bearing nude mice models and evaluation of the possible toxicities initiated after GS2 treatment. In addition, for a half-century, many scientists have synthesized hundreds of new Platinum-based complexes and tested them as anticancer drugs, among them carboplatin and oxoplatin worldwide recognized, and satraplatin and picoplatin are in various stages under clinical investigations. All of these drugs have similar structures, where one or more platinum atoms coordinated to amine or amine carrier ligands with chloro, carboxylate, oxalato, or acetate leaving groups. Their mode and action such as prevention of DNA transcription and replication leading to cellular apoptosis are the same and they are all susceptible to the development of drug resistance and display severe dose-limiting toxicities[6]. The disadvantage of cisplatin treatment includes not only the side effects associated with its inherent toxicity at pharmacological levels but also the gradual acquired cellular resistance to therapy. Most metal-based pharmaceuticals today are constructed with carbon-based ligands. These ligands, which often are multifunctional in nature, are needed to ensure the protection of tissues from toxic metal ions, to maintain or re-establish healthy homeostasis, and to precisely target particular tissues or enzymes. Taking into account, that both kinetic and thermodynamic variables in ligand and complex design allow for fine-tuning of a metal-based or metal-targeting molecule, whether for therapeutic or diagnostic use, so under these circumstances, it is important to modify the ligand for the biological effects of metal-based drugs[11,12]. L-cysteine is a protein amino acid that exists naturally, as a protein in most living organisms, a large part of the platinum reacts with the cysteine groups of proteins instead. Therefore, the platin-cysteine drug is the most preferable to other anticancer drugs but these reactions induce the toxic side effects that occur in cancer chemotherapy. These reactions with sulfur-containing proteins are associated with cellular resistance against platinum drugs[13,14]. For removing the resistance, glutathione is widely used with cisplatin but it may be replaced by thiols or nucleobases[15]. Whereas the Pt-cysteine bond is considered to be kinetically more inert[16]. It was suggested by Rauter et al. that only one chloride-leaving group on each platinum can remove the resistance[17]. Coinage metals such as gold, silver, and copper demonstrated catalytic activity in organic synthesis[18] and exhibited stronger and/or Lewis acidity, making Au(I) catalysts acceptable and feasible for diverse types of transformations such as the hydrofunctionalization of alkynes and cycloisomerization of enynes/multiynes. Silver(I) has been intensively exploited to activate gold catalysts through anion metathesis (counterion exchange); whereas copper salts prefer to function as versatile catalysts for oxidative coupling reactions via a single electron transfer process. Moreover, silver and copper are both extensively used salts as outer-sphere oxidants. We have been interested in developing original aromatic-nonaromantic-sulfur-platinum complexes Platinum(II)DTHBAC that inhibit the growth of cancer cells.

Proposed drug modeling and design:

We have chosen cysteine derivative ligand, the head is 3, 5-Di-tert-butyl-2-hydroxy-benzylamine (DTHBA), and the tail is cysteine. The two t-butyl groups of DTHBA can facilitate DTHBA partition in a hydrophobic pocket of the membrane[19], which may be inhibited like zinc-containing proteolytic enzyme carboxypeptidase (Figure 1). The 2-hydroxy group of DTHBA has the capability to donate a proton. In fact, it is an electron donor and most likely renders more electronegative to the hydroxy group at position 2 in the aromatic ring of DTHBA. It might be hypothesized that the electronegative hydroxy group of DTHBA interacts with a positively charged Pt cation. Our hypothesis may discover a suitable ligand for the platinum complex, which will be more useful as an anticancer drug without any side effects.

Synthesis of the 3,5-ditert-butyl-2-hydroxy-benzylamino-cysteine (DTHBAC) may be a molecular mimicry model for the generation of new active drugs, that creates with a cysteine group and two tertiary butyl groups attached to the aromatic ring of phenol can be coordinated with a metal (Pt), generating products with activity and selectivity for some cancer cell lines. This synthesis can be designed in two consecutive stages:

I. The solid sample of cysteine (1.0mmol) was dissolved in 10ml H_2O. Aqueous NaOH 5ml (1.1 mmol) and 37 % aqueous formaldehyde (10 mmol) were added to the solution and stirred for 20 minutes at room temperature then 10ml ethanol solution of 2,4-di-tert-butyl-phenol (1.0 mmol) was added drop by drop. The reaction mixture was then heated for 5 hours in an oil bath at 50°C. When the reaction solution was cooled to room temperature and it was allowed to stand overnight. The precipitate was filtered and washed with water and hexane. The precipitate was taken in methanol solution and acidified with aqueous hydrochloric acid. The white solid obtained from vacuum evaporation was washed several times with acetonitrile and dried under vacuum at ambient temperature.

II. Cis-Platinum(II)$(NH_3)_2Cl_2$ (1.0 mmol) dissolved in 5 ml dry methanol was added drop by drop to 10ml methanolic solution of HL (1.0mmol) and (mmol) methanolic solution of NaOH and stirred. After 1 hour, a crystalline powder was collected by filtration and dried in a vacuum under pressure (Figure 2).

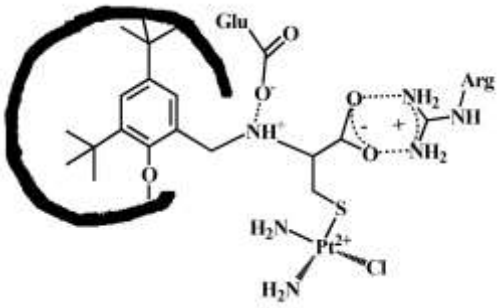

Figure 1: *N*-substituted cysteine derivatives as potential inhibitors

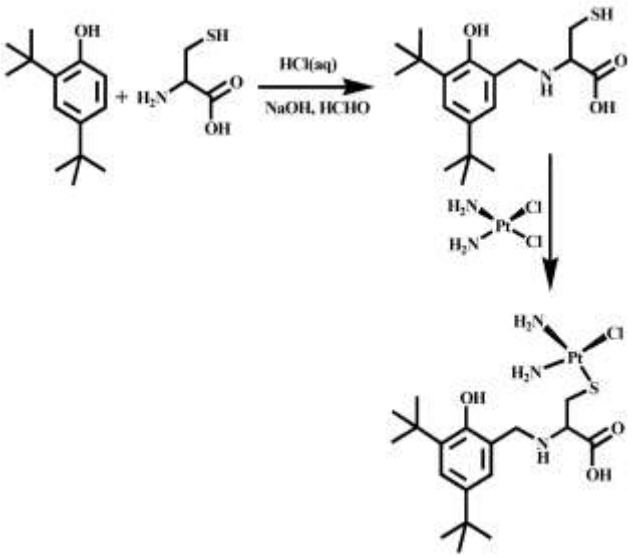

Figure 2: Schematic diagram of ligand and complex synthesis

The agents capable of modulating multiple targets in a selective manner can improve the balance between clinical and therapeutic benefit and safety compared to the characteristics of unique target-directed agents, and that is the advantage of multi-target directed[20,21]. An attempt was made by Graur et al[22] to synthesize the ligand 1-(2-hydroxyphenyl)ethanone N(4)-allyl-3-thiosemicarbazone where they synthesized six coordination compounds of copper, nickel, and cobalt with this ligand and established that the substitution of the hydrogen atom with a methyl group in the azomethinic fragment leads to the growth of antitumor activity. Nevertheless, cancers are multifunctional disorders. Thus, different cancers have different features, and therefore, it is unlikely to find one cure to treat all cancers by targeting only one specific gene product or one pathway required for tumor growth. Moving forward, combinatorial strategies that target multiple mechanisms, such as reducing cisplatin uptake and reducing inflammation, may offer the best chance for clinically meaningful prevention.

Rationality:

Medical research has, in recent years, focused on elucidating the mechanisms underlying cancer and developing new techniques that identify perturbations of cell functions. In cancer chemoprevention, malignancy is able to be prevented by blocking, hindering, or reversing tumorigenesis by employing agents. Usually, platinum complexes are clinically used as adjuvant therapy for cancers, aiming to induce tumor cell death and also for the treatment of a spectrum of specific cancers; including testicular, ovarian, bladder, head and neck, esophageal, small and non-small cell lung, breast, cervical, stomach, and prostate cancers, Hodgkin's and non-Hodgkin's lymphomas, neuroblastoma, sarcomas, multiple myeloma, melanoma, and mesothelioma, etc. An alternative approach can be advantageous for enhancing the permeability of tumor blood vessels and the inefficient lymphatic drainage in tumors. Macromolecular diffusion out of blood vessels is facilitated in the tumor region, so any drug delivered by an agent can accumulate in the tumor and persist for long periods of time. Therefore, understanding the mechanisms triggered by cisplatin 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. Moreover, molecular mechanisms behind the modulation of cellular responses will be needed to develop and optimize new therapeutic strategies. Thus, the design of this hypothetical drug model will be more effective than the existing medicine for cancer treatment and will add a new dimension to the cancer treatment system. Significantly, the hydrophobicity of the targeted cancer cells is used to capture the nonpolar portion of the affected cells, which is present in the designated molecule's aliphatic surface chain, can overcome the chloride resistance for the future action of other drug molecules, and can be easily destroy the cancer cells. However, there may be some major gaps that need to be filled in order to understand fully the delicate interplay between molecular factors that promote either death of the cancer cell or survival of the resistant phenotype, and hence extensive research is necessary in order to improve anticancer treatments and to decrease toxic effects.

Conflict of interest:

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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