Metal-Based Chemotherapy Drugs

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Abstract: Metal-based compounds have been used to treat disease since as early as the 5th and 4th century B.C. Cisplatin, a platinum-based chemotherapy drug, was one of the first metal-based compounds found to treat cancer. Other platinum drugs such as oxaliplatin and carboplatin have been the backbone of metal-based cancer treatment drugs as well. The potential therapeutic benefits of metal complexes, in particular, transition metals, has gained attention due to exhibiting unique characteristics including their capability to go through a redox reaction. Due to limitations like drug resistance and worsening side effects, ruthenium compounds have been developed that caused less severe and fewer side effects. Copper complexes have been found to exhibit cytotoxic properties with distinct mechanisms of actions and even have the ability to competitively bind to sites occupied by different metals. It has been suggested that gold complexes have the potential to possess antitumor properties if cisplatin cannot be used as a form of treatment. Silver complexes are another potential type of chemotherapeutic drug, found to exhibit greater selectivity against cancer cells and display better cytotoxic action than cisplatin with comparably low toxicity. The potential for metal-based chemotherapy drugs is continually expanding, and more research should be carried out in order to learn all of the benefits these unique drugs have to offer the world.

Introduction

> "Everything is poisonous, and nothing is harmless. The dose (amount) alone defines whether something isn't poison"
> Paracelsus, 1493-1541.

There is currently a broad scope of anticancer agents that targets numerous biological and cellular characteristics across multiple tumor types. The evolution of anticancer drugs has shifted away from traditional cytotoxicity and in the direction of selective agents which act on particular cellular targets. Nonetheless, considerable challenges linger, and the link between chemistry and structural biology may supply the most productive method for improving upon and discovering anticancer agents.

In nature, numerous biological systems utilize metal ions, for instance, copper and zinc, which perform crucial roles in the natural functioning of organisms. Transition metals including manganese, copper, and iron, among other transition metals, are involved in several biological mechanisms, from structural roles to catalysis to electron transfer, and are regularly associated with the active sites of enzymes. Dysregulation of several of these metals during regular biochemical processes has been involved with the incidence of numerous pathological disorders, including cancer. These cellular activities only need small, tightly regulated amounts of "trace metals." In comparison, other metals including nickel, chromium, cadmium, and arsenic are not as advantageous because those metals generate a broad range of severe toxic side effects, such as carcinogenesis (Arita and Costa, 2009, Rahman and Singh, 2019).

Throughout history, numerous metal-containing compounds have been used to treat a broad array of disorders. In medicinal chemistry,

which has generally been influenced by organic chemistry, metal-containing compounds have acquired favor as anticancer agents and diagnostic tools. The study of metal-containing anticancer agents began with the accidental discovery of the anticancer properties of cisplatin, cis-[PtII(NH_3)$_2$$Cl_2$]. The clinical use of cisplatin is limited as a result of resistance along with a confined spectrum of activity and dose-dependent toxicity. Because of these limitations, there has been an exploration for platinum-based complexes that demonstrate a wider spectrum of activity, higher selectivity, and lower toxicity; cisplatin and carboplatin emerged because of this research. Nonetheless, along with various platinum analogs, several other metal compounds consisting of metal ions, for instance, copper chelating agents, gold, silver, copper(II), and zinc(II) have gained abundant attention as possible anticancer agents. In addition, the analysis of ruthenium-containing complexes in clinical trials vouches for the vast potential of using non-platinum metal-based complexes for cancer treatment (Dabrowiak 2012, Franklin and Costello 2009, Ajmal 2017). This review examines the function of chosen metals in biological mechanisms within cells as they relate to malignancy as well as feature the medical uses of those metals and their structures in the development and design of metallodrugs for cancer treatment.

Exceptional Features of Metal-Based Complexes and Metal Ions

Medicinal inorganic chemistry is a promising and constantly evolving field that involves several processes including, but not limited to, the introduction (or expulsion) of an ionic metal into (or out of) an organism in order to diagnose or to provide therapeutic effects. Because metals have the ability to become cations when submerged in aqueous solution and bond to biological molecules with a negative charge, charge manipulation can be achieved contingent upon the coordination environment influencing the production of a cationic, ionic, or neutral biological molecule. Furthermore, metal ions displaying high electron affinity have the capability to polarize groups coordinated with them, which allows the production of hydrolysis reactions (Haas and Franz, 2009). Due to these properties of metals, the potential therapeutic use of medicinal inorganic chemistry in the construction of anticancer agents has recently gained significant interest.

Throughout ancient history, metals have been used in various medical treatments. The earliest written account of metals being used for medical treatment dates back to 1500 BC when Ebers Papyrus wrote about how iron could be used to treat anemia and how Copper could be used to decrease inflammation (Dabrowiak, 2012). Metals have the ability to treat cancer by being able to collaborate precisely with DNA and to specifically attack cancer cells. Since the phosphate backbone of DNA is negatively charged, the positive charge of almost all metals gives metals the ability to interact with DNA. A number of drugs manufactured that contain metals communicate precisely with separate metals that are already available at the protein active sites. Other drugs developed have the ability to make metals communicate with amino acids that have the largest reduction potential. Even though metals have been used since ancient times, the full potential of metal-based chemotherapy drugs was not realized until the discovery of cisplatin during the 1960s. It is well known that the existence of metals in cellular conditions is a heavily regulated process, therefore precise doses of drugs containing metals need to be established in order to attain an optimum therapeutic response. If precise administrations of metal-containing drugs are not established, then a deficiency or excess of metals could develop undesirable toxicity.

In comparison to conventional carbon-based compounds, metal-containing compounds present several benefits in the expansion of modern medicinal compounds. These benefits exist because of the metal-containing compounds capability to integrate ligands within a three-dimensional configuration, which allows the functionalization of groups which can be tailor-made to carefully defined molecular targets (Frezza et al., 2010). Metal-based compounds present a well-supplied environment to assemble a wide range of specific molecular structures

which deliberate an ample range of geometries and coordination numbers, including kinetic properties, which could not be accomplished with traditional carbon-based compounds (Frezza et al., 2010). Fascinating electronic features that have the ability to act as applicable probes in the composition of anticancer agents are due to the partly filled d orbitals that occur in metals. When looking at the design of coordination compounds, it is essential to recognize the oxidation state of a metal due to the fact that it grants participation in the biological redox chemistry and has a significant function in the optimum dosage and the bioavailability of agent distribution. In addition, the capacity of metals to participate in ligand-exchanged reactions proposes endless opportunities for coordination and interaction to occur between metals and biological molecules, exhibited by the broad medicinal use of cisplatin. When constructing metal-based drugs, one is not confined to choosing only certain metals; advantage can be taken of the special characteristics of nonessential metals, along with other first and second-row transition metals, including metals that are not found naturally (Haas and Franz, 2009). Most momentous is the composition of radiopharmaceuticals which have the ability to employ the radioactive features of metals and are frequently operated within diagnosing cancer and separate medicinal treatments.

Platinum-based analogs in chemotherapy

The history of the first metal-based chemotherapy drug begins not in 1965 as many people believe, but in 1844, during which time it was originally developed by Michele Peyrone and known as Peyone's chloride (Wheate and Apps, 2015). The extraordinary breakthrough was made in 1965 was by Barnett Rosenberg, a biophysical chemist, when he accidentally discovered cisplatin could be used as a treatment for cancer. The discovery of the therapeutic use of cisplatin in cancer therapy encouraged efforts to explore non-platinum and additional platinum metal-containing compounds that could potentially be employed in cancer treatment. Cisplatin has been broadly utilized to treat an assortment of tumors including testicular, non-small cell lung carcinoma, head, and neck, cervical and ovarian cancers, and is often employed in combination regimens (Kelland, 2007). The widespread clinical use of cisplatin has been impeded by the presence of acquired and intrinsic resistance and increased toxicity. In order to overcome these problems, there have been 2nd and 3rd generation platinum drugs developed, mainly oxaliplatin and carboplatin, which have the ability to maintain a much more controllable toxicity profile (Alama et al., 2009). Oxaliplatin has been clinically authorized as a treatment for colorectal cancer, which has shown to be resistant to cisplatin, while carboplatin has been shown to be an effective treatment for head and neck, lung, and ovarian carcinoma cancers (Frezza et al., 2010).

One of the main reasons platinum-based compounds have such a practical antitumor effect has to do with the platinum-based compounds ligand exchange kinetics. The ligand exchange behavior of platinum-based compounds is moderately slow, even though the platinum-ligand bond presents comparable thermodynamic ability and is considerably weaker than classic coordination bonds, like C-O, C-N, or C-C double and single bonds. Due to the ligand exchange behavior being rather slow, this gives platinum-based compounds a lofty kinetic stability and grants exceptionally prolonged ligand exchange reactions to the point where it can take minutes to days to complete instead of seconds (Reedijk, 2003). In addition, regarding Pt(II) compounds, ligands that are located in the trans arrangement are substituted much more quickly than ligands in the cis arrangement, which plays an important part in the antitumor efficiency of these compounds(Frezza et al., 2010). Cisplatin is known to go through ligand substitution reactions and rarely expands its coordination number. Through active or passive transport, cisplatin is absorbed through cells and its chloride ions will be replaced with molecules of water prior to interacting with DNA, thus making coordinative bonds to the nitrogen atoms in DNA (Fuertes et al., 2003). The resulting elevated chloride ion concentration in blood plasma allows cisplatin to be stable regarding hydrolysis, but the lower concentration of intracellular chloride facilitates accelerated

hydrolysis toward the activated cationic molecule that can bind DNA (Pizarro and Sadler, 2009). It has been found that carboplatin has a much more advantageous pharmacokinetic profile due to its delayed conversion rate to the reactive species of carboplatin (Frezza et al., 2010). Carboplatin has a similar mechanism of actions when compared to cisplatin, therefore problems remain when carboplatin is used to treat tumors that are resistant to cisplatin. Replacing the chloride group located on cisplatin by the cyclobutanedicarboxylate ligand located on carboplatin provides better stability and adequate aqueous solubility (Frezza et al., 2010). This then induces decreasing side effects, while maintaining a comparable degree of cross-resistance towards cisplatin and clinical activity.

At the time platinum-based compounds bind to cells in the body, miscellaneous signal transduction pathways undergo activation, which then acts to intervene with various cellular processes including DNA replication and transcription, thereby causing apoptotic cell death. In comparison to cisplatin and carboplatin, the hefty diaminocyclohexane (DACH) carrier ligand located on oxaliplatin has been thought to grant lower cross-resistance and a better toxicity profile (Frezza et al., 2010). In 2002 the FDA approved oxaliplatin, often combined with chemotherapy, for treating advanced colon cancer.

Throughout the years, research into platinum-based medicine has been heavily influenced by the medicinal use of carboplatin, cisplatin, and recently oxaliplatin. Researchers have been conducting innovative methods with the goal of creating the next era of platinum-based drugs due to continual issues with resistant and toxicity in current platinum-based drugs. The fundamental information learned from platinum(II) compounds, along with resistance mechanisms and cellular processing, harnessed with an enhanced insight towards mechanisms of action might assist in translating the upcoming generation of platinum-based medicinal compounds into clinical practice.

Two big concerns that started the pursuit of innovative platinum-based coordination compounds attention to oral administration were low bioavailability and poor solubility of clinically accepted platinum compounds (Frezza et al., 2013). While platinum(II) chemistry depends upon ligand exchange reactions, platinum(IV) has octahedral geometry that offers two excess ligand locations and the elevated kinetic inertness of platinum(IV) diminishes reactivity, which then has the ability to diminish off-target effects (Hall et al., 2007). Most evidence indicates platinum(IV) complexes are decreased in vivo to form platinum(II), which is the compound that is accountable for its stimulation and can be treated as a pro-drug (Frezza et al., 2010). Satraplatin, an octahedral platinum(IV) compound that is given orally and is in progressive clinical stages for the medicinal therapy of hormone refractory prostate cancer, is the most distinguished example originating from this group (Frezza et al., 2010). Platinum(IV) compounds demonstrate benefits due to their bioreductive activation and greater stability, hence letting a large amount of drug to arrive at its biological target. It has been shown that the anti-tumor action of satraplatin works similarly to cisplatin due to the development of inter and intrastrand DNA cross-links (Choy et al., 2008).

Powerful strides have been made regarding the field of platinum-based chemotherapy drugs, especially concerning mechanistic comprehension of these drug's pharmacological effects and design strategies. Advancing our current knowledge of platinum-based compounds, including resistance mechanisms, tumor uptake, and structure-activity-relationship (SAR) can assist the progress of the medicinal installation of the next era of platinum-based chemotherapy compounds.

Zinc

Zinc is known as a crucial trace element performs an integral function in a broad scope of cellular processes especially with regards to protection against free radicals, cell proliferation, and differentiation. Zinc operates as a crucial anatomical element in several enzymes and proteins, including DNA repair enzymes, cellular signaling proteins, and transcription

factors (Roohani et al., 2013).

It has been found that zinc performs a crucial function in regulating apoptosis within mammalian cells, although it is not completely understood how it does this. In several cell types, including ovarian epithelial cells, glial cells, prostate epithelial, and other cells, zinc has been shown to activate apoptosis, while in Hela cells, macrophages, renal cells, lung epithelial cells, and breast cells, zinc has been shown to have antiapoptotic effects (Franklin and Costello, 2009). These conflicting developments have been subjected to extreme investigation and still, remain unanswered.

Since zinc plays a crucial role in countless biochemical systems, it is unsurprising that altered amounts of zinc are correlated with systemic anomalies, including the incidence of cancer. Even though it has been found that concentrations of zinc are compromised in patients suffering from cancer in comparison to healthy patients, the relation between zinc levels and tumor developments lacks recognizable conclusions and depends on the type of tumor (Frezza et al., 2010). Patients suffering from prostate, digestive tract, gallbladder, or liver cancer have been found to have reduced zinc levels, while patients suffering from breast cancer exhibited elevated and decreased levels of zinc in malignant tissues and serum (Frezza et al., 2010). Emerging evidence has suggested that the expression levels of zinc transports are related to cancer progression (Zhao and Eide, 1996). Altered expression of zinc transporters could perform an important function in the incidence of cancer by interrupting function and intracellular distribution. Along with the crucial duty, zinc has in biological systems, its unique characteristics have granted it to acquire approval as probable anticancer agents.

Copper

Copper is a fundamental trace metal that is important in various biochemical processes including angiogenesis, development, cellular growth, and chemical redox reactions. In biological systems, copper is found as both (Cu+) or (Cu2+), which allows copper to act as a cofactor for redox reactions. In order to avoid unneeded binding to biomolecules, ensure distribution and proper uptake, the procurement and dispersion of copper is a highly controlled process. Notably, the coordination chemistry associated with copper is usually distinct dependent on its oxidation state: Cu+ displays favoritism towards sulfur donor ligands, for example, methionine or cysteine, while Cu2+ exhibits a preference for nitrogen donors, for instance, histidine or oxygen donors including aspartate or glutamate (Frezza et al., 2010).

The relationship between copper and carcinogenesis has been intensely investigated over the past two decades. The reason for this was because it was discovered that tumor-bearing humans and mice possess altered copper levels; studies found that elevated tissue and serum levels of copper were present in several human tumors including brain, lung, colon, prostate, and breast, in comparison to healthy individuals (Frezza et al., 2010). The reason for the elevated levels of copper has not yet been fully understood and no conclusions have been made.

The idea of antiangiogenic therapy utilizing copper chelators in the treatment of cancer has received abundant attention because of the discoveries concerning the significance of copper and angiogenesis in tumor development (Frezza et al., 2010). Considerable clinical trials have begun and have demonstrated encouraging results (Redman et al., 2003). It is known that elevated copper concentration and raised proteasome activity are distinct characteristics found in tumor-bearing humans. Frezza et al. (2010) found that these particular aspects associated with tumors cells have the ability to be utilized as distinct targets by previously clinically authorized drugs that perform as effective tumor cell killers when those drugs form a complex with copper.

Ruthenium

Because of limitations like drug resistance and worsening side effects to platinum-based drugs in the treatment of cancer, the focus has shifted toward the development and design of

practical non-platinum-based drugs, including gold and ruthenium that are less harmful to normal cells, with less resistance and enhanced efficiency (Ajmal, 2017). Ruthenium-based compounds have distinct characteristics, such as the ability to reside in a larger amount of spatial positions in comparison to cisplatin, a larger amount of probable accessory molecules which can be transported by the drug arrangement and in particular, the likelihood to prevail in the organic fluids of nearly all of the most crucial oxidation states ranging from oxidation state II to IV (Popolin et al., 2017). All of these unique properties have made ruthenium-based compounds encouraging antimetastatic and antitumor candidates. Popolin et al. (2017) discovered [$Ru(CH_3CO_2)$(dppb)(bipy)]PF6 [where bipy = 2,2'-bipyridine and dppb = 1,4-bis(diphenylphosphino)butane] as a possible treatment for triple-negative breast cancer (TNBC) due to its ability to more efficiently inhibit the proliferation of TNBC cells over normal, non-tumor cells, inhibit TNBC cells migration and invasion, adhesion, and to cause the death in TNBC cells, although this complex should be studied in vivo to establish its potential to help improve the treatment for breast cancer.

Silver

Since ancient times, it has been known that silver is an effective antimicrobial agent against a wide range of microorganisms. Currently, silver is used to regulate bacterial growth in medical settings, including the mending of burn wounds, catheters, and dental work (Jung et al., 2008). Silver nanoparticles (AgNPs) comprise a category of materials that range from 1-100nm. Recently AgNps have been reported to adjust Pgp activity and consequently improve the chemotherapeutic efficiency against cancer cells that are multi-drug resistant (Abdel-Fattah and Ali, 2018). Furthermore, the genotoxicity displayed by AgNPs is backed by the production of breaks in double-stranded DNA in addition to chromosomal instability which encourages the start of apoptotic execution (Abdel-Fattah and Ali, 2018). This acting mechanism indicates that AgNPs could be correlated with various DNA-targeting anticancer drugs.

Saratale et al. (2017) made AgNPs from Taraxacum officinale, also known as the dandelion, and demonstrated its enhanced cytotoxic impact against human liver cells stricken with cancer (HepG2). Biofunctionalized AgNps made within separate plant extracts of clove and guava displayed the satisfactory anti-cancer impact against four separate cancer cell lines including human chronic myelogenous, human colorectal adenocarcinoma, concerning the human kidney, leukemia, human cervix and bone marrow (Abdel-Fattah and Ali, 2018). Aydin et al. (2014) were able to demonstrate that two silver-containing metal complexes, $C_{16}H_{34}N_8O_5Ag_2$ Cd (AN1) and $C_{11}H_{16}N_7O_2Ag_3$ Ni (AN7), have the ability to act as effective anticancer drug candidates that demonstrate low cytotoxic, higher antiproliferative, strong apoptosis-inducing and efficient DNA topoisomerase inhibitory traits, although additional in vivo and in vitro studies must be carried out in order to verify the anticancer drug potential of AN1 and AN7.

Gold

In order to attain a more advanced cytotoxicity profile demonstrating a broader range of activity in comparison to platinum-based compounds, the chemotherapeutic ability of gold coordination complexes has been investigated. Studies have demonstrated that communications of DNA, the favorable destination of platinum, with gold(III) complexes failed to present an advantageous binding mode, accelerating the research into gold and protein interactions (Frezza et al., 2010). In the beginning, studies concentrated on an array of artificial gold(III) diothiocarbamate derivatives which were revealed to demonstrate 1-to-4-fold more cytotoxicity than cisplatin and had the ability to substantially overcome acquired and intrinsic resistance (Ranconi et al., 2005). Still, these studies were unable to demonstrate a molecular link among the gold compounds and their chemotherapeutic activity. A study done by Frezza et al. (2010) featured the proteasome as a crucial molecular destination of gold complexes but exhibited apparent mechanisms of action that are responsible for its fundamental biological actions, which rely upon the metal's oxidation state.

Conclusion

The crucial role metals perform in the maintenance and functioning of life features the extensive role nature plays in managing these essential components. The clinical achievements of cisplatin paved the road for researching metals, nonessential or essential, and those metals coordination complexes as possible anticancer agents. Since the chemotherapeutic effects of cisplatin were discovered, thousands of platinum-based compounds have been made, with only oxaliplatin and carboplatin accomplishing widespread clinical use. Construction methods of novel platinum compounds have been intensely investigated in order to focus on the defects of past generation platinum compounds.

Cisplatin was the first widely used metal-based chemotherapy drug, but due to drawbacks including the presence of acquired and intrinsic resistance, and increased toxicity, the search for other metal-based chemotherapy drugs has expanded. Oxaliplatin and carboplatin are 2nd and 3rd generation platinum drugs that have been developed in response to this and have a much more controllable toxicity profile. Several non-platinum-based drugs have been suggested including zinc, copper, gold, silver, and ruthenium, among others. The altered expression of zinc transporters could perform an important function in the incidence of cancer by interrupting function and intracellular distribution. Because it is known that elevated copper concentration and raised proteasome activity are distinct characteristics found in tumor-bearing humans, utilizing copper chelators in the treatment of cancer has received abundant attention as well. Due to limitations like drug resistance and worsening side effects, ruthenium compounds have been developed that caused less severe and fewer side effects. It has been suggested that gold complexes have the potential to possess antitumor properties if cisplatin cannot be used as a form of treatment. Silver complexes are another potential type of chemotherapeutic drug, found to exhibit greater selectivity against cancer cells and display better cytotoxic action than cisplatin with comparably low toxicity. Because metals are equipped with unique characteristics that are not present in common carbon-based medicines, the positive trend associated with the discovery of anticancer drugs can persist by advancing the fundamental knowledge acquired from the study of medicinal inorganic chemistry. The potential for metal-based chemotherapy drugs is continually expanding, and more research should be carried out in order to learn all of the benefits these unique drugs have to offer the world.

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Submitted June 5, 2019 Accepted November 12, 2019