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Extended Abstract

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Progress on the design of metal-based drugs for cancer therapy

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Statement of the Problem: Research on the field of metal-based compounds for the treatment of cancer diseases has attracted increasing interest due to the urgency to find more efficient and selective treatments than the platinum-based drugs in clinic use. In this frame, ruthenium compounds hold a prominent position due to the success of NAMI-A and KP1019 in progressing through clinical trials. Nevertheless, this progress has been retarded due to problems concerning their aqueous instability and complicated ligand exchange chemistry, characteristic of inorganic complexes. As alternative, rutheniumbased organometallic compounds are proposed as viable alternatives to circumvent the disadvantages of platinum-based drugs, since their cytotoxicity might involve different modes of action and, in many cases, present reduced toxicity profiles.

Methodology & Theoretical Orientation: During the last decade, our research group has been developing cyclopentadienyl-ruthenium (RuCp) based compounds that revealed important cytotoxicity against different cancer cell lines surpassing cisplatin in activity. In vivo studies for one of our leads on a highly metastatic breast cancer (MDA-MB-231, a model for triple-negative breast cancer) revealed a dual effect by suppressing primary tumor growth and inhibiting the formation of metastases. The present communication overviews the progress in our work toward the development of new organometallic metal (II) drugs mainly based on ´RuCp` and ´FeCp` scaffolds. Moreover, our latest studies on other families of new compounds based on Ru (III) complexes bearing NN, NO and NS bidentate ligands will be also presented.

Conclusion & Significance: The results presented herein offer valuable and convincing evidence for the relevance of metal-based compounds as future anticancer therapeutic agents. The overall rationale on the design of these new families of compounds envisages finding possible correlations between structural features and biological activity to guide forthcoming work. Thus, chemical properties and structural features of each compound are intended to be correlated with its biological effects. metal-based compounds were widely used in the treatment of disease conditions, but the lack of clear distinction between the therapeutic and toxic doses was a major challenge. With the discovery of cisplatin by Barnett Rosenberg in 1960, a milestone in the history of metal-based compounds used in the treatment of cancers was witnessed. This forms the foundation for the modern era of the metal-based anticancer drugs. Platinum drugs, such as cisplatin, carboplatin and oxaliplatin, are the mainstay of the metal-based compounds in the treatment of cancer, but the delay in the therapeutic accomplishment of other metal-based compounds hampered the progress of research in this field. Recently, however, there has been an upsurge of activities relying on the structural information, aimed at improving and developing other forms of metal-based compounds and nonclassical platinum complexes whose mechanism of action is distinct from known drugs such as cisplatin. In line with this, many more metal-based compounds have been synthesized by redesigning the existing chemical structure through ligand substitution or building the entire new compound with enhanced safety and cytotoxic profile. However, because of increased emphasis on the clinical relevance of metal-based complexes, a few of these drugs are currently on clinical trial and many more are awaiting ethical approval to join the trial. In this review, we seek to give an overview of previous reviews on the cytotoxic effect of metal-based complexes while focusing more on newly designed metal-based complexes and their cytotoxic effect on the cancer cell lines, as well as on new approach to metal-based drug design and molecular target in cancer therapy. We are optimistic that the concept of selective targeting remains the hope of the future in developing therapeutics that would selectively target cancer cells and leave healthy cells unharmed. Arsenic trioxide (ATO) was used as an antiseptic and in the treatment of rheumatoid diseases, syphilis and psoriasis by traditional Chinese medical practitioners. Certainly, ATO was among the first compounds suggested for use in the treatment of leukemia during 18th and 19th centuries, until in the early 20th century when its use was replaced by radiation and cytotoxic chemotherapy. Therapeutic use of gold and copper can be traced to the history of civilization, where the Egyptians and Chinese were famous users in the treatment of certain disease conditions, such as syphilis. The discovery of platinum compound (cisplatin) by Barnett Rosenberg in 1960s was a milestone in the history of metal-based compounds used in the treatment of cancer. This forms the foundation for the modern era of the metal-based anticancer drug. Despite the wide use of the metal-based compounds, the lack of clear distinction between the therapeutic and toxic doses was a major challenge. This was so because practitioners of ancient time lack adequate knowledge of dose-related biological response. The advent of molecular biology and combinatorial chemistry paves the way for the rational design of chemical compounds to target specific molecules. Generally, metals are essential components of cells chosen by nature. They are frequently found in the enzyme catalytic domain and are involved in multiple biological processes, from the exchange of electrons to catalysis and structural roles. They are extensively used in cellular activities. Such metals include gallium, zinc, cobalt, silver, vanadium, strontium, manganese and copper, which are required in trace amounts to trigger catalytic processes. To this end, a balance between cellular need and the amount available in the body is important for the normal physiological state. Comparatively, metals, including nickel, cadmium, chromium and arsenic, can induce carcinogenesis and hence are less beneficial to the body. These limitations have triggered a search for platinum-based compounds that show lower toxicity, higher selectivity and a broader spectrum of activity.

Platinum (II) complexes such as carboplatin and oxaliplatin as well as other platinum analogs are the products of this search. Other metal complexes containing ions such as zinc (II), gold and copper chelating agents have received considerable interest as anticancer agents. Recently, the chemistry of ruthenium and gold-based compounds has received intensive scrutiny, due to renewed interest in providing an alternative to cisplatin, because of their promising cytotoxic and potential anticancer properties. Nevertheless, metal-based compounds, especially transition metals, exhibit definite properties including their potential to undergo a redox reaction. Therefore, metals and their redox activities are tightly regulated to maintain normal wellbeing. Recently, there has been a growing demand for metal-based compounds in the treatment of cancer. This may be due to the scourge of cancer and, to the greater extent, the level of in vitro cytotoxic effect exhibited by metal-based compounds, particularly those synthesized recently. In addition, ligand substitution and modification of existing chemical structures led to the synthesis of a wide range of metal-based compounds, some of which have demonstrated an enhanced cytotoxic and pharmacokinetic profile. Again, a different approach of cytotoxic drug design has recently been adopted. This involves conjugating metallic compounds with bile acid, steroid, peptide or sugar to allow direct drug delivery to the cancer cells, thereby circumventing some pharmacokinetic challenges. The objective of this review is to provide an overview of previous reviews on the cytotoxic effects of metal-based compounds while focusing more on newly designed metal-based compounds and their cytotoxic effect on the cancer cell line, as well as on new approach to metal-based drug design in cancer therapy.

Bottom Note: *This work is partly presented at* 6th World Congress on NATURAL PRODUCT & SYNTHETIC CHEMISTRY June 24-25, 2019 | New York, USA.