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Mini review

Using Tin Compounds as Cancer Chemotherapy Drugs

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Introduction

Cancer or the big 'C' is a complex disease and one of the alarming health concerns of mankind (the global economic toll is 20 percent higher in cancer than other major diseases *viz*., cardiovascular diseases, cerebrovascular diseases, HIV/AIDS, lower respiratory infection including pneumonia, malaria, and cirrhosis, as well as road accidents). Globally, there is a rise in cancer incidence which is predicted to increase from 14 million new cases in 2012 to 22.2 million in 2030 [1]. The primary treatment modalities for cancer include surgery, chemotherapy, radiations and immunotherapy etc. However, the mainstay treatment is based on chemotherapy that involves the use of various chemical entities (natural and synthetic) that have the potential to kill or check the unwanted proliferation of cancerous cells [2]. In this milieu, cisplatin (cis-diamminedichloroplatinum (II)) and its second generation analogues, *viz*. carboplatin and oxaliplatin, have received worldwide clinical acceptance in treating testicular, ovarian, small cell lung and colorectal cancers. Despite their success, the challenges of platinum drugs regarding toxicity, intrinsic resistance and narrow spectrum of activity for phenotypes of cancers derived from multiple etiologies have motivated researchers to focus on other non-platinum drugs. A substantial investigation of other metals as antitumor chemotherapeutic agents which include transition metal ions (Ti, Fe, Co, Cu, Au, Zr, Ru and Zn) and non-transition metal ions (Sn and R_2SnX_2) has been undertaken to overcome the problems of toxic side effects and resistance [3].

Metal-based anticancer drugs have various potential advantages: [1] (i) a wide number of coordination geometries, (ii) accessible redox states, (iii) tunability of thermodynamics and kinetics of ligand substitution and (iv) attacking several sites (multi-targeting) which can be a highly effective strategy for drug design. It is also important to identify these target sites and elucidate the molecular mechanism of action. The strategies for rational drug design can be envisaged by studying the interactions of small molecules with DNA and also their reaction at specific sites along a DNA strand. Much attention has been directed towards the design of metal-based cancer chemotherapeutics, the design of new metal-based pharmaceuticals depending on the ligand framework and the choice of metal ion.

Tin (IV) compounds were proven as outstanding class of novel antitumor and antiproliferative agents; much of the earlier work has been carried out by Crowe (1989), Crowe and Fricker (1994), Gielen (1995) and Nebojsa et al. (2020) which has been published and also patented [3]. Among the tested Tin (IV) compounds, exhibited a wide spectrum of biological activity, and have gained tremendous impetus because there *in vitro* antitumor activity is greater than the *in vivo* activity of cisplatin –a well-known cancer drug especially used for its promising pharmacological profile. Tin (IV) and Organotin (IV) complexes also have some properties such as increased water solubility, lower general toxicity and fewer side effects than platinum drugs [4]. The cytotoxic activity of organotin (IV) compounds are greatly influenced by; (i) the hydrolysable groups (X) attached to Sn atom which controls the delivery of the active $RnSn^{n+}$ species (ii) the organic group (R), the ligand (L) and the number of tin atoms and the number of free coordination positions offered appear to play an important role in their antiproliferative action of the compounds. Undoubtedly, complexes derived from tin and organotins with modulated ligand scaffold could bring hope to mortality and morbidity of mankind caused by rapidly spreading cancers [5]. Additionally, organotin (IV) complexes are known to act as strong apoptotic directors, activating apoptosis directly *via* p53 tumor suppressor. Apoptosis is known as programmed cell death and represents also a control mechanism within the cell that reacts to the changes in its surrounding environment [6]. This active cellular death process is characterized by distinctive morphological changes that include condensation of nuclear chromatin, cell shrinkage, nuclear disintegration, plasma membrane blebbing and the formation of membrane-bound apoptotic bodies. Tin (IV) and organotin compounds are involved in cancer treatment *via* different mechanisms at the molecular level and most of the tin complexes are DNA target. The phosphate group of DNA sugar backbones usually acts as an anchoring site and nitrogen of DNA base binding is extremely effective, this often resulting in the stabilization of the tin center as an octahedral species. Literature revealed that tin-based complexes exhibit pronounced cytotoxicity against human cell lines *viz*., ID_{50} values (63 ng mL^{-1} against MCF-7 and 121 ng mL^{-1} against WiDr cell line as compared to 600 and 976 ng mL-1, respectively for cisplatin) and further, it has also been demonstrated that these complexes induce apoptosis *via* mitochondrial genemediated pathway [5]. In contrast to apoptosis, organotin (IV) compounds can induce cancer cell apoptosis by triggering DNA damage, thus leading to activation of various apoptosis pathways through p53 tumor suppressor pathway. Almost five decades of wagging war against big 'C' cancer have passed since the development of cisplatin and taxol (pacitaxel); both these compounds being the 'magic bullets' for treatment of cancers, in addition to other major antitumor drug regimes in clinical use [6]. Today, most chemotherapeutic strategies involve a combination or cocktail of drugs incorporating bioactive pharmacophores and a recognition element. Such combinations need to be investigated for the best of the organotin compounds. It is probable that the organotins intersect cancer growth at different venues than other classical anticancer drugs so these combinations might prove quite useful.

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