



## Highlighting the Journey So Far with Cancer and Chemotherapy

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**Received:** April 17, 2020

**Published:** May 22, 2020

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### Abstract

Cancer is one of the most deadly diseases in the world with thousands of deaths occurring globally from the disease. Despite several interventions, chemotherapy has proven to be one of the most effective treatment patterns used for majority of cancer types. This review is aimed at emphasizing the current updates with cancer chemotherapy suggesting the potentials for a new set of chemotherapy agents in cancer treatment.

**Keywords:** Cancer; Chemotherapy; Disease; Treatment

### Introduction

Cancer can be described as a disease that involves a group of abnormal cells growing out of control, disregarding the normal patterns of cell division [1]. Ideally, normal dividing cells are constantly regulated by cues that dictate whether the cells should divide, differentiate into another cell, or undergo apoptosis [1]. Overtime, cancer cells become resistant to these signals, becoming autonomous to cell growth and division prompts, and consequently leading to uncontrolled cell division, growth and proliferation [1,2]. Over 10 million new cases of cancer are reported each year, and cancer-related deaths are projected to increase in the near future with an estimation by the World Health Organization of approximately 13 million cancer-related deaths by the year 2030 [2]. Generally, cancer cells are believed to develop from normal cells due to damage of DNA. Typically, when DNA becomes damaged, the body is able to repair it. Unfortunately, in cancer cells, damaged DNA isn't repaired and occasionally can be inherited [3].

### History and causes of cancer

Cancer has been recognized for several hundred years, with its earliest description in a book titled "Cautions against the immoderate snuff" written by physician John Hill [4]. The book was published in 1761 as a result of scientific findings which observed that tobacco snuff caused "polypus" which was described as a small vascular growth on the epithelium of a mucous membrane [4]. No significant studies had been made till over two decades later when Hill's findings paved the way for new studies on cancer epidemiology where it was noted that tobacco smoking caused lung cancer

[4]. The first occupational link to cancer was reportedly established in 1775 when Sir Percivall Pott of Saint Bartholomew's Hospital in London wrote an essay that linked soot leads to high incidence of scrotal cancer in young men that worked as chimney sweeps which he then referred to them as the chimney-sweepers' cancer [5]. No significant studies on carcinogens cancer causing agents, were published till the early 20<sup>th</sup> century when two Japanese investigators developed the first animal assay for carcinogens. They repeatedly applied coal tar on the skin of rabbit ears, which resulted in the development of tumors after a few weeks. Subsequently, the rats and mice were found to be more responsive to the carcinogen [4]. Over the years, many compounds and mixtures have been recognized as potential human carcinogens. Numerous findings have illustrated that asbestos, chromium, nickel and arsenic compounds, vinyl chloride, aflatoxins and most notably tobacco smoke are potential carcinogens [6]. It has also been reported that there is a high rate of cancer occurrence in patients with viral infections from Hepatitis B and C virus, human papillomavirus (HPV), as well as human immunodeficiency virus (HIV) that have contributed to cases of liver cancer, lymphomas, carcinomas, and nasopharyngeal cancers [1,3]. Prolonged sun exposure is a factor causing skin damage, due to increased exposure to ultraviolet rays from the sun; the fast rise in tanning salons have also fostered the increased rate of skin cancers (melanomas) [7].

### Cancer treatment and prevention

Findings have suggested that the risk of getting cancer can be minimized by lifestyle changes and modifications [1,8]. Primary

cancer prevention strategies encouraged includes quitting smoking and minimizing alcohol consumption [8]. Likewise, diet modification through the incorporation of fruits and vegetables as well as a high fiber diet can help reduce the incidence of stomach and colon cancer [1,9]. Currently used treatment for cancer includes surgery, radiation, chemotherapy and sometimes hormonal blocking [10]. Surgery becomes an ineffective process in cancer treatment when the tumor has spread to different parts of the body. Radiation therapy, although effective, is also limiting because healthy cells are harmed in the process, and therefore, newer radiation machines that concentrate the energy to only cancerous cells are being considered currently in use [5,11]. Chemotherapy involves the use of anticancer medications. In particular, this therapy is often prescribed when cancerous cells have spread widely in the body, but most times a combination of such medications works better than a single medication [5]. Cancer chemotherapy has also been reported to achieve partial or complete response where either half or all of detectable cancerous cells are eliminated. The set back of chemotherapy use is the development of drug resistance by cancerous cells over time [12].

### Cancer chemotherapy

A famous German Chemist Paul Ehrlich coined the word “chemotherapy” and defined it as the use of chemicals to treat disease [5]. Chemotherapy works by killing rapidly dividing cells, halting their growth and spread or slowing down their development. Chemotherapy can, however, affect healthy cells, leading to unwanted side effects [13]. The use of various metal based compounds in treatment of several diseases is dated to ancient times due to their therapeutic properties [14]. Metals are part of numerous biological activities, such as reaction catalysts, and structural functions to the exchange of electrons in cells. They are often situated in the enzyme catalytic domains and are profoundly employed in cellular activities. These metals are often needed in just trace amount to facilitate catalytic events in the cell [15]. In spite of the prevalence of metal-based compounds in the treatment of diseases since ancient times, lack of appropriate dosage was a major drawback associated with its use. Medical experts at that time had little or no knowledge about dose-related biological response, but the emergence of cell biology, molecular biology, and biochemistry paved way for the design of metal based compounds to target specific molecules in the cell [16].

The advent of platinum based compound cisplatin in 1960 by Barnett Rosenberg [17], was a major advancement in the use of metal based compounds in the treatment of cancer cells. This major breakthrough was considered the foundation for develop-

ment of modern day metal based anticancer drugs [17]. Distinctive features of metals such as reactivity towards organic substrate, variable coordination modes, and redox activity have enhanced their use in cancer therapy [14]. These unique characteristics were the attractive site of metals in the model of Metal complexes that binds to the biomolecular target with a resultant disruption in the mechanism of cell proliferation ultimately leading to death of the cells. The recent groups of metal based synthesized compounds are designed to achieve higher levels of cytotoxicity and lesser side effects that could not be achieved with the compounds already in use [18]. Generally, platinum compounds, particularly cisplatin, are the most prevalent of the metal based compounds used in cancer chemotherapy [19]. Platinum complexes act as an adjuvant in cancer treatment to facilitate apoptosis or programmed cell death [13]. These metal complexes are mostly recommended for the treatment of ovarian, testicular, breast, ovarian, prostate and lung cancers [20].

For over three decades now, platinum based anticancer drugs, including cisplatin and its analogues, have dominated the treatment of cancers by chemical events [19,21]. The discovery of cisplatin (cis-diaminedichloro-platinum(II)) decades ago marked the beginning of a tremendous development in the production of platinum based anticancer drugs [13]. Cisplatin is a very efficient anticancer drug, with several positive results against testicular, ovarian, bladder tumors, as well as head and neck malignancies [22]. Research has indicated that cisplatin is usually administered intravenously rather than orally because of its low solubility in water [17,22]. The mechanism of cisplatin action is by passive diffusion [23] and the cytotoxicity of cisplatin is believed to arise from its binding to DNA and the formation of covalent cross-links [23]. Binding of cisplatin to DNA then causes alteration of helical structure and results in halting of DNA replication and transcription [24]. The disrupted DNA structure can be used as a recognition or binding site for cellular proteins such as repair enzymes, transcription factors, histones and high-mobility group (HMG) proteins [25]. The process of binding of the HMG proteins to cisplatin-DNA lesions has been suggested to facilitate the antitumor activity of the drugs [26]. The anticancer property of cisplatin is also influenced by the efficiency of cisplatin-DNA adduct removal by the cellular repair machinery, with nucleotide excision repair being a major pathway [23,27]. Another commonly used platinum based drug is, carboplatin (diamine[1,1-cyclobutanedicarboxylato(2-)]-O,O'-platinum (II)) [28]. The basic pharmacokinetic differences between cisplatin and carboplatin depend primarily on the slower rate of conversion of the latter to reactive species. Regarding the interaction of carboplatin with DNA, results from studies provide

evidence that the reaction is initiated via ring-opening in carboplatin and subsequent binding with DNA constituents. The side effects of using carboplatin is also described as minimal when compared with cisplatin, and the drug is said to be better tolerated by the body and can be used at higher prescription doses than cisplatin [29]. Oxaliplatin is another platinum based anticancer drug that has been approved for use against cancer cells that do not respond to cisplatin. Its mechanism of action is not completely understood, but it is believed to interact with DNA in a similar way to cisplatin and carboplatin. Oxaliplatin can be employed for the use with other medications against the treatment of advanced colorectal cancer [29].

Platinum and palladium are believed to have similar physical and chemical properties. The significant similarity between the coordination chemistry of palladium (II) and platinum (II) compounds has triggered the studies of Pd (II) complexes as antitumor drugs [29]. Likewise, hydrolysis of palladium is about  $10^5$  times faster than its platinum counterpart, which enables it to dissociate instantly in solution and ultimately is unable to reach its pharmacological targets [21]. Research has indicated that one of the methods to improve the biological activity of Pd (II) complexes is its combination with selected ligands that will significantly decrease the rate of hydrolysis at the metal site [30]. Several studies have focused on the preparation of Pd (II) complexes bearing bidentate ligands as a way to stabilize these compounds and to prevent any possible cis-trans isomerism [31].

### Reactive oxygen species and chemotherapy

Reactive oxygen species (ROS) has been described as unstable, reactive, partially reduced oxygen derivatives that are generated as an end product of metabolism. They include hydrogen peroxide ( $H_2O_2$ ), superoxide anion ( $O_2^-$ ), singlet oxygen ( $^1O_2$ ), hydroxyl radical ( $\cdot OH$ ) and sometimes peroxynitrites ( $ONOO^-$ ) [32], that acts as a borderline between reactive oxygen and reactive nitrogen species. They are believed to act as secondary messengers in cell signaling and are essential for various biological processes in healthy and diseased cells [32]. Altering of ROS levels is a mechanism shared by most chemotherapeutics due to their effect in promoting programmed cell death [33]. In cancer cells, ROS levels are increased due to both environmental and internal mechanisms. The overall balance of ROS and the combined positive and negative effects of ROS all contribute to the final impact on cancer biology [34]. Most chemotherapeutics generate ROS in cancer cells, and findings from several studies indicate that chemotherapeutic amplification of ROS levels pushes the already increased cancer cells over a threshold to cause cell death and is one of the proposed mechanisms by

which multiple chemotherapies foster tumor regression [34,35]. Anthracyclines, such as doxorubicin, daunorubicin and epirubicin, are believed to produce the highest levels of cellular ROS [36]. Platinum coordination complexes, alkylating agents and camptothecins are said to also generate high levels of ROS [37].

Studies further revealed that two major reasons are attributed to increased ROS levels in chemotherapy; elevation of mitochondria ROS generation and suppression of the cellular antioxidant system [32,38]. Antibiotics based chemotherapeutic agents such as anthracyclines, doxorubicin, bleomycin, and platinum coordination complexes, also target the mitochondria and induce cellular ROS generation [38]. Studies also indicate that reactive oxygen and nitrogen species play key roles in cancer initiation and survival, by modifying tumor growth through numerous cellular and molecular events such as DNA damage and genome instability [39]. Nitric oxide (NO) is a bioactive molecule generated by NO synthases (NOSs) in mammalian cells. By interacting with numerous diverse biomolecules, NO and its derivatives are engaged in a broad range of cellular responses, from neurotransmission to regulation of vascular tone to immune responses and tumorigenesis [40]. In majority of cancers, NOS activity has been implicated with increased tumor growth, malignant transformation, angiogenesis and most notably resistance to apoptosis [41]. Research pointed out that there is a strong correlation between the prevalence of tumor cells generating inducible NOS (iNOS; i.e. NOS2) and shortened survival of patients with advanced skin cancer [42]. Inhibition of NO production by cisplatin *in vitro* was indicated to act synergistically with reduction in tumor development and increased sensitivity to cisplatin [43]. Several pathways are believed to be activated after treatment with chemotherapeutics; The PI3K/AKT pathway is believed to be frequently mutated in human cancers [44]. Chemotherapeutic agents like cisplatin are believed to trigger cancer cell apoptosis and autophagy through dose-dependent stimulation of ROS-MAPK signaling [45].

### Recent findings

A currently studied group of ligands called cyanoximes, is the common name for a family of compounds with the general formula  $NC-(C=N-OH)-R$ , where R is an electron-withdrawing group [46]. Cyanoximes have been described as outstanding ligands with unique biological properties such as growth regulation, antimicrobial and detoxification activities [46,47]. In line with the idea of further exploration of new, non-traditional platinum complexes, cytotoxic bivalent Pd and Pt complexes with deprotonated MCO and PiPCO ligands were shown to possess *in vitro* activity comparable to cisplatin [47]. These square-planar Pd and Pt complexes

represent the first group of active, novel oxime-based bis-chelates. However, prior to the above studies, no high-yield preparations of Pd, Pt-cyanoximates were developed, no direct structural information about these complexes was available, and their electronic structure was not fully understood [30]. Studies have revealed that cyanoximes are excellent ligands for a strong binding of a variety of metal ions in formed complexes, and they are considered much better ligands than traditional aldoximes and ketoximes [48]. The anti-proliferative activity and cytotoxicity of cyanoximes and their metal complexes have not been properly studied. The first bivalent palladium and platinum cyanoximate was synthesized, characterized and described by several authors [49]. This paper studied the *in vitro* effect of two MCO- based complexes of Pd and Pt on the anti-proliferating activity of human cervical cancer HeLa cell lines with cisplatin as a positive control. The study stated that Pd(MCO)<sub>2</sub> caused 28% death, and its platinum analogue Pt(MCO)<sub>2</sub>, yielded 16% death [49]. A follow up studies highlighted the *in vitro* biological activity of bivalent Pd and Pt cyanoxime complexes with ligand derivatives of substituted cyan-acetamides abbreviated as HPiPCO and HMCO [30]. In this study, Pd(MCO)<sub>2</sub> and Pt(MCO)<sub>2</sub> were tested at varying concentrations against both HeLa (cervical cancer) and WiDr (colon cancer) cell lines. The cytotoxicity study found that Pt(MCO)<sub>2</sub> and Pd(MCO)<sub>2</sub> affected HeLa cells greatly at 1.0 mM concentrations showing a 42 ± 3% and 45 ± 3% cell death, respectively. The findings were comparable to values obtained with cisplatin, at 1.0 mM, which was used as a positive control, showing a 56 ± 5% cell death against HeLa cells. Both Pt(MCO)<sub>2</sub> and Pd(MCO)<sub>2</sub> affected the wellbeing of WiDr cells, causing 73 ± 9% and 81 ± 11% cell death respectively at 1.0 mM. At the same concentration, cisplatin caused a 64 ± 1% of cell death under the same conditions [30]. A recent findings in Dr. Gerasimchuk's lab emphasized the synthesis of a new group of cyanoximates; platinum and palladium DECO, (DECO:2-cyano-2-oxiamino-N,N'-diethylaminoacetamide), Bis (2-cyano-2-oxiamino-N,N'-diethylaminoacetamide) platinum (Pt(DECO)<sub>2</sub>) and Bis (2-cyano-2-oxiamino-N,N'-diethylaminoacetamide) palladium (Pd(DECO)<sub>2</sub>) [50]. Owing to previous and ongoing studies, the newly synthesized cyanoximates reveals possible potentials for a new anti-cancer agent in chemotherapy.

## Conclusion

The discovery of cancer has warranted research into different treatment regimes. With chemotherapy being one of the most widely used, it is relevant to provide updated information about the current state of research about chemotherapeutic agents.

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