

Platinum-based agents in oncology and strategies for tumor suppression

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ABSTRACT

The discovery of the anticancer properties of platinum derivatives by Rosenberg represents a notable progression in the development of chemotherapeutic approaches for tumor management. In 1978, cisplatin was the first platinum-based drug to gain approval from the Food and Drug Administration for the treatment of testicular cancer, along with advanced ovarian and bladder cancer. Platinum-based drugs, including cisplatin, carboplatin, and oxaliplatin, are widely employed in chemotherapy for cancer treatment. Cisplatin is widely used in the treatment of solid tumors, such as those found in the bladder, ovarian, lung, gastric, breast, cervical, and head and neck areas. Platinum-based drugs engage with cancer cells through interactions with DNA, resulting in alterations to the double helix structure. This interaction interferes with the mechanisms of DNA transcription and replication, leading to the eventual induction of cell apoptosis. The effectiveness of anticancer treatment using platinum-based medications is regrettably limited by the development of resistance. The negative consequences linked to platinum-based medications include issues with selectivity, considerable systemic toxicity, and the emergence of drug resistance, in addition to nephrotoxicity, ototoxicity, myelosuppression, and peripheral neurotoxicity. As a result, to tackle the resistance and toxic effects, alternative platinum derivatives are utilized, taking

advantage of progress in nanotechnology and chemical synthesis. Nanodrugs that contain platinum, such as platinum nanoclusters, demonstrate novel anti-cancer mechanisms and are employed in the treatment of different cancer types.

INTRODUCTION

Rosenberg identified the anti-cancer properties of platinum derivatives (1-3). This discovery represents a significant advancement in the evolution of chemotherapeutic approaches for cancer treatment (5). Cisplatin, the pioneering platinum-based drug, received approval from the Food and Drug Administration for the treatment of testicular cancer, advanced ovarian cancer, and bladder cancer (4). Platinum-based agents like cisplatin, carboplatin, and oxaliplatin are extensively utilized in the chemotherapeutic treatment of cancer (3). Cisplatin is a platinum-based chemotherapeutic agent primarily utilized in the treatment of solid tumors, including those located in the bladder, ovaries, cervix, lungs, breasts, stomach, and head and neck. Cisplatin-based chemotherapy for testicular cancer is regarded as nearly curative (4). Cisplatin and carboplatin, both platinum derivatives, have gained worldwide clinical approval and are essential components in most chemotherapy protocols for cancer treatment (5). The efficacy of platinum-based anticancer therapies is constrained by the emergence of resistance. The results reveal a range of negative impacts, including diminished selectivity, heightened systemic toxicity, and the development of drug resistance. Cisplatin is associated with nephrotoxicity and ototoxicity, carboplatin is recognized for inducing myelosuppression, and oxaliplatin is connected to peripheral neurotoxicity (6). The toxicities impose considerable constraints on dosage and negatively impact the quality of life for those who have overcome cancer. To address resistance and reduce toxic effects, new platinum derivatives and contemporary application strategies have been developed. Recent advancements in nanotechnology and chemical synthesis have significantly enhanced the efficacy of platinum-based anti-cancer drugs in the treatment of cancer. Platinum-based nanodrugs, such as platinum nanoclusters, exhibit novel anti-cancer mechanisms and show

significant potential for application in targeted tumor therapy. Cisplatin, a first-generation platinum-based anti-cancer drug, was discovered in the late 1960s and received approval for cancer treatment in 1978 (29). Cisplatin shows therapeutic efficacy against various malignant tumors, including breast, ovarian, and colorectal cancers (18). Cisplatin is a compound that causes systemic toxicity in addition to its cytotoxic actions on tumor cells. The prolonged administration of cisplatin results in significant harm to normal tissues. Consequently, the advancement of the second-generation platinum chemotherapy agent carboplatin occurred. Carboplatin, characterized by its reduced toxicity, is appropriate for application as high-dose chemotherapy in managing aggressive tumors. The administration of cisplatin and carboplatin often leads to the development of drug resistance during the treatment process. Consequently, the formulation of the third generation platinum compound, oxaliplatin, was achieved. Oxaliplatin functions in a manner akin to cisplatin; however, it does not induce cross-resistance with either cisplatin or carboplatin (36-37). Oxaliplatin and cisplatin exhibit a synergistic effect and are extensively utilized in cancer treatment (38-40). Among the diverse range of anti-cancer platinum agents, multifunctional high-performance platinum nano cluster-based (Pt NC-based) nanodrugs, developed from various biocompatible materials leading to versatile designs, have garnered significant interest for targeted cancer therapy and drug delivery [22, 23]. In contrast to conventional first-line platinum-based chemotherapeutics, Pt NC-based nanodrugs demonstrated enhanced stability, superior water dispersibility and solubility in vitro, along with reduced systemic toxicity and improved biocompatibility in vivo [24-26]. The distinctive benefits of Pt NC-based nanodrugs, including controllable fabrication, biosafety, and anti-tumor efficacy, underscore their significant potential for application in cancer treatment [27].

Molecular Mechanism of Cisplatin

Platinum-based anti-cancer agents, including cisplatin, carboplatin, and oxaliplatin, are extensively utilized in cancer treatment. Cisplatin primarily impacts cancer cells

by interfering with their DNA replication and transcription processes. Cisplatin predominantly enters tumor cells via the copper transporter 1 (CTR1). Upon entering the tumor cell, the platinum complex undergoes an activation step, during which the chloro-ligand is replaced by water molecules or other small molecules containing sulfhydryl groups. The concentration of chloride ions within cells is approximately 4 mM, significantly lower than the concentration outside the cells, which is about 100 mM. The decreased concentration triggers the replacement of chloride ions and promotes the transformation into cationic hydrates, such as $\text{cis-[Pt(NH}_3\text{)}_2\text{Cl(OH}_2\text{)]}^+$ and $\text{cis-[Pt(NH}_3\text{)}_2\text{(OH}_2\text{)}_2\text{]}^{2+}$ [34]. The hydration rate and reaction with ammonia for transplatin occur significantly faster than those of cisplatin. The complex is swiftly rendered inactive prior to reaching its designated target, owing to the considerable reactivity of transplatin. Following a sequence of chemical reactions in the cytoplasm, the activated platinum complex binds to DNA, resulting in the formation of intra- and inter-stranded crosslinks. The structure of DNA is altered, resulting in damage and obstructing the processes of replication and transcription [36, 37]. Cisplatin primarily engages with the N7 position of guanine, which is easily accessible in the major groove and is preferentially involved in platinating reactions. DNA damage can disrupt the cell cycle and trigger apoptosis in rapidly proliferating tumor cells [38, 39].

Pt Nanoparticles (PtNPs) as a New Pt Drug for Cancer Therapy

Platinum nanoparticles (PtNPs) find applications in the diagnosis and treatment of cancer, along with addressing multi-drug resistance in bacteria (Jabir et al., 2012). Nanotechnology is utilized to address bacterial antibiotic resistance and assist in tumor management (Taylor and Webster, 2011). PtNPs incorporate hydrophilic polymers that improve opsonization, while MNPs are employed in cancer treatment (Jabiretal., 2012). Platinum exhibits significant anti-cancer characteristics (Reedijk, 1987). PtNPs exhibit distinct mechanisms of action when contrasted with platinum-based pharmaceuticals, while demonstrating comparable

efficacy in anticancer activity. PtNPs demonstrate cytotoxic effects in cancer cells via passive diffusion or endocytosis, with their effectiveness influenced by size, concentration, and incubation duration. The cytotoxicity primarily results from the induction of strand breaks in chromosomal DNA (Porcel et al., 2010; Johnstone et al., 2016; Kutwin et al., 2017). DNA damage interferes with replication processes and triggers cell cycle arrest as well as apoptosis. Another mechanism of platinum nanoparticles (PtNPs) involves the inhibition of cellular metabolic activity, the generation of hydroxyl radicals, and the release of active free Pt^{2+} ions; this strategy is currently employed in radiotherapy. PtNPs exhibit antioxidant properties at specific concentrations (Asharani et al., 2010; Gehrke et al., 2011; Prasek et al., 2013). Furthermore, PtNPs have the potential to enhance the host's anti-tumor immune response by improving antigen presentation and activating T cells (Yu et al., 2022). PtNPs demonstrate significant photostability following multiphoton stimulation within cellular contexts, making them suitable for imaging and microscopy purposes (Botchway et al., 2008). López Ruiz et al. (2020a) developed a unique dendritic structure composed of silver (Ag) and platinum (Pt) nanoparticles. AgPtNPs demonstrated a notable inhibitory effect on drug-resistant pathogenic bacteria such as *P. aeruginosa*, *E. coli*, and *S. aureus*, exhibiting greater efficacy than silver NPs. PtNPs underwent coating with PA (PA/PtNPs) to enhance targeted delivery to bone. The investigation explored the combined effects of photothermal therapy (PTT) and the anticancer properties of PA in malignant bone cancers (Zhou et al., 2019). Phytic acid (PA) is a polyphosphorylated carbohydrate that is frequently encountered in fiber-rich human diets, particularly in legumes and cereals, and is found in most mammalian species (Wilson et al., 2013). This shows enhanced effectiveness in addressing malignant bone tumors. Platinum nanodrugs that employ nanocarriers have garnered significant interest because of their extended blood circulation duration, enhanced permeability and retention (EPR) effect, and ease of surface functionalization.

CONCLUSION

Traditional tumor chemotherapy utilizes chemotherapeutic agents that frequently result in significant negative impacts on normal cells and tissues [13]. Platinum-based anti-cancer agents are essential in clinical oncology, demonstrating significant effectiveness. Cisplatin and other first-line clinical platinum-based anti-cancer agents are established treatments that show efficacy against tumors through clearly defined molecular mechanisms. The negative consequences significantly restrict the use of platinum-based anticancer agents. Investigations have been conducted on modified Pt-based drugs to assess their potential in enhancing anti-cancer efficacy while minimizing systemic toxicity. Pt NC-based nanodrugs have garnered significant interest owing to their extended blood circulation duration, enhanced EPR effect, and ease of surface functionalization. Recent advancements in nanotechnology and nanoscience have enabled the development of platinum nanoclusters (Pt NCs), which play a vital role in the investigation of platinum-based drugs designed with specific structures to enhance therapeutic efficacy and minimize systemic toxicity [27]. Therapeutic drugs derived from platinum have been extensively studied for their ability to target and eliminate tumor cells. The use of these chemotherapeutic agents presents considerable difficulties, as their dose-dependent acute and chronic side effects stem from their non-selective impact on both tumor and healthy cells. Recent advancements in eco-friendly nanomaterials have significantly impacted various fields, such as energy applications, electronics, biomedical engineering, and drug delivery. Platinum nanoparticles (NPs) represent a category of metal NPs that exhibit numerous benefits, including anti-tumor and anti-bacterial characteristics, which render them useful in a range of pharmaceutical applications.

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