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Metal-Based Drugs in Cancer Therapy

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Abstract: Metal-based drugs have emerged as pivotal therapeutics in cancer therapy, enlightening a path toward innovative and effective treatment strategies. Platinum-based therapeutics, notably cisplatin, carboplatin, and oxaliplatin, have transformed the landscape of cancer treatment, setting the stage for the development of next-generation metal-based compounds. This article explores the design of metal-based drugs, including their complex coordination chemistry, tailored drug delivery strategies, and mechanisms of action. Notably, metal-based compounds form covalent bonds with DNA, disrupting vital cellular processes and inducing apoptosis in cancerous tissues. Even though contemporary chemotherapy, as well as radiotherapeutic methods, have greatly increased patient survival rates, disease recurrence still represents a fatal danger. The probability of metastasis and drug resistance is increased by the incomplete clearance of neoplastic tissues from the body. This review explores the compelling journey of metal-based compounds like platinum, ruthenium, and copper, from their historical significance to their pivotal role in modern oncology. Also, it discusses the recent advancements and emerging trends that promise to shape the future of metallodrugs. While looking into the mechanism of action of these drugs, it was revealed that in addition to producing reactive oxygen species (ROS), metal-based drugs also impede enzyme functions and bind DNA to exert their anti-cancer effects. The shining promise for metal-based drugs in cancer remedies holds the potential to revolutionize treatment paradigms, offering hope and resilience in the ongoing battle against one of humanity's most relentless adversaries.

Introduction

Cancer, a relentless and formidable adversary, has persistently plagued humanity for centuries (Cox et al., 2021). Based on the most recent data, cancer accounts for one out of every six disease-related deaths; more specifically, one-fifth of men, as well as one-sixth of women, is detected with malignancy during their lifespan; one in eight males and eleven women pass away from it. Australia and New Zealand dominate the world in terms of cancer incidence and death rates, followed by North America and Europe (Siegel et al., 2023; Adhikari et al., 2024). Over the years, this complex disease has grown exponentially, leading to remarkable advances in cancer diagnosis and treatment (Bhattacharjee and Mukherjee, 2016; Das et al., 2021; Boga and Bisgin, 2022; Sen et al., 2022; Kesavan et al., 2023; Kulkarni et al., 2023). Among the myriad therapeutic approaches, the advancement of metal-based medications has emerged as a beacon of hope, promising a shining future in the battle against cancer (Saha and Yadav, 2023; Das et al., 2023; Solairaja et al., 2023). Historically, metal compounds have played a pivotal role in medicine, dating back to ancient civilizations where metals like Au, Cu, and Fe were employed for their healing properties (Norn et al.,2008). However, it is only in recent decades that the true potency of metal-based drugs in cancer treatment has

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come to the forefront. These compounds exhibit a unique combination of chemical versatility, biological activity, and structural diversity, making them invaluable in pursuing innovative cancer treatments (Sarma, 2016; Adhikari et al., 2019; Nath et al., 2022; Mehta et al., 2023; Rami et al., 2023).

The roots of metal-based drugs in medicine can be traced back to ancient times when the Egyptian and Greek civilizations used metals such as Cu and Fe for their curative properties (Norn et al., 2008). Copper, for instance, was employed to treat wounds and infections, while iron was used to combat anemia. These early observations hinted at the therapeutic potential of metals in medicine. Despite the widespread usage of metal-based drugs, it was difficult to distinguish between levels that were therapeutic and hazardous. This was because ancient practitioners lacked a basic understanding of dose-related physiologic responses. The detection of the anti-cancer traits of Pt-based compounds marked a vital moment in the history of metal-based medications. In 1965, cisplatin, a Pt-containing compound, was seen to display remarkable cytotoxic activity against cancer cells, ushering in the era of Pt-based chemotherapy (Rosenberg et al., 1971). Cisplatin's success made it possible to develop further Pt-based medications, like oxaliplatin and carboplatin, which have become cornerstone treatments for various types of cancer (Dilruba et al., 2016). However, the emergence of side effects such as nephrotoxicity, neurotoxicity, and cytotoxicity has limited the therapeutic usage of Pt-based drugs (Ndagi et al., 2017). The lack of therapeutic specificity, the ineffective accumulation of medicines at tumor sites, and the development of drug resistance are the fundamental problems of cancer therapy (Ulldemolins et al., 2021). Consequently, as prospective substitutes, novel metal-based anti-cancer medications are being researched. These include metallodrugs with a customized drug delivery mechanism (Dissanayake et al., 2017). The historical journey of metallodrugs from ancient therapies to modern cancer therapies underscores their enduring relevance in the medical field. Researchers are looking forward to developing novel metal-based compounds that have better antitumor properties and fewer adverse effects than cisplatin.

Principles of designing metal-based drugs

Most transition metals have unpaired electrons and have variable valency. Metal complexes derived from transitional elements have inimitable physicochemical characteristics that make them useful in bioinorganic chemistry for cancer treatment. The design of metallodrugs is a meticulous process that combines chemistry, biology, and pharmacology to develop compounds capable of selectively targeting and destroying cancer cells while sparing healthy ones. This therapeutic selectivity is critical to minimizing side effects and improving patient outcomes.

Several key principles govern the design of these promising agents:

Coordination chemistry

At the heart of metallodrugs is coordination chemistry, which explores the interaction between metal ions and ligands. By carefully selecting ligands and metal ions, researchers can fine-tune the chemical properties of metal-based drugs, influencing their stability, reactivity, and biological activity (Adhikari et al., 2019; Adhikari et al., 2020; Adhikari et al., 2020; Adhikari et al., 2020; Adhikari et al., 2021; Adhikari et al., 2023; Bhattacharjee et al., 2022; Bhattacharjee et al., 2022; Ghosh et al., 2006; Ghosh et al., 2006; Ghosh et al., 2006; Ghosh et al., 2008; Ghosh et al., 2008; Ghosh et al., 2008; Ghosh et al., 2011; Ghosh et al., 2017; Park et al., 2012; Park et al., 2012; Singh et al., 2017; Singh et al., 2018).

Targeted delivery

To enhance the selectivity of metal-based drugs for cancer cells, researchers have developed innovative delivery strategies. These approaches include encapsulating metal-based drugs in nanoparticles or conjugating them with targeting molecules that recognize cancer-specific biomarkers (Das et al., 2023; Das et al., 2023; Gavas et al., 2021). Such techniques reduce off-target effects and increase drug accumulation in tumors.

Mechanisms of action

Metal-based medications exert their anti-cancer influences *via* diverse mechanisms, including DNA binding and inhibition of enzymatic processes, besides generating reactive oxygen species (ROS) (Boros et al., 2020). Understanding these mechanisms is crucial for tailoring drug design to specific cancer types and achieving optimal therapeutic outcomes.

Overcoming resistance

Drug resistance to chemotherapeutic measures is a noteworthy hurdle in managing cancer (Wang et al., 2019). Metal-based therapeutics, with their unique mechanisms of action, offer potential solutions to this problem (Bhattacharjee et al., 2022). They can target cancer cells that have become resistant to traditional therapies, providing a lifeline to patients facing limited treatment options. Traditionally, patients receiving the dose of chemotherapy or targeted medication could be treated for cancer. It was discovered this type of treatment could accelerate the onset of drug resistance

since it continuously forces tumors to select cancer cells that are highly resistant to the drugs. Longer life and delayed drug resistance were the results of new treatment tactics that involved "on and off" or "high dose followed by low dose." This is because adaptive or intermittent dosing can prevent the development of drug-dependent resistant cells and promote the competition of sensitive and resistant cells (Kaiser, 2017; Nath et al., 2024).

Platinum-based anti-cancer drugs: Evolution from past to present

Pt-based anti-cancer drugs have revolutionized the field of oncology since their discovery in the 1960s (Table 1) (Ghosh, 2019). With cisplatin as the pioneer, these Pt-based compounds have become essential weapons to combat various forms of malignancy. The Pt-based anti-cancer drugs began with the unexpected discovery of cisplatin by Barnett Rosenberg and his colleagues in 1965 (Rosenberg et al., 1971). Rosenberg was conducting experiments regarding the influences of electric fields on bacterial growth and witnessed that Pt electrodes inhibited cell division (Rosenberg et al., 1965). This accidental discovery led to the synthesis of cisplatin, which soon revealed its remarkable cytotoxic properties. Cisplatin was the first Pt-based drug to be permitted for medical utilization, marking a groundbreaking moment in the history of cancer therapy (Wiltshaw et al., 1979). In 1978, approval was given by the FDA for treating testicular malignancy was given. Its success opened the door for developing new Pt-based compounds, viz., carboplatin and oxaliplatin, that have expanded the repertoire of available treatments for various cancer types.

The effectiveness of Pt-based anti-cancer therapeutics lies in their capability to interfere with DNA replication and cell division (Rabik et al., 2007). These drugs form covalent bonds with purine bases in DNA, primarily guanine, leading to the formation of DNA adducts. This binding disrupts the DNA double-helix and inhibits the transcription and replication of genetic information. Consequently, cancer cells are unable to divide and proliferate, eventually undergoing apoptosis or cell death (Zorbas et al., 2005). Cisplatin, carboplatin, and oxaliplatin share this fundamental mechanism of action, making them effective against a vast range of neoplastic growths. However, differences in their chemical structures and reactivity profiles contribute to variations in their toxicity and range of activities.

Carboplatin

This is a second-generation Pt-based drug that offers reduced toxicity compared to cisplatin (Kelland, 2007). In the 1980s, researchers sought to develop Pt-based drugs with reduced side effects in comparison to cisplatin. This led to carboplatin synthesis, which exhibits a more favorable toxicity profile while retaining anti-cancer activity (Iwasaki et al., 2005). Carboplatin became a noteworthy drug for treating ovarian as well as lung malignancies, among others, and its use continues to evolve in combination therapies.

Oxaliplatin

Oxaliplatin emerged in the 1990s as a third-generation Pt-based drug (Mathe et al., 1986). Oxaliplatin was designed and synthesised in order to circumvent the resistance mechanisms shown in cisplatin and carboplatin. Oxaliplatin was successful in treating colorectal cancer, often combined with other chemotherapeutic agents, and it remains a critical component of modern cancer treatment regimens (Graham et al., 2000). It has a distinctive mechanism of action, which includes the DNA adducts formation and interference with DNA repair mechanisms.

Clinical impact and challenges

Platinum-based therapeutics have shown a profound influence on the treatment of malignancy, significantly raising survival rates besides improving the quality of life for many patients. They are used for a diverse type of cancer, viz., testicular, ovarian, lung, bladder, and colorectal malignancy, among others. However, challenges persist:

Resistance

Malignant cells can become resistant to Pt-based drugs over time, limiting their long-term efficacy. Researchers are actively studying the mechanisms of resistance and developing strategies to overcome them, including combination therapies with other drugs (Zhou et al., 2020).

Side effects

While Pt-based drugs have proven effective, these often cause side effects like kidney damage, neuropathy, and nausea (Cornelison et al., 1993). Efforts to minimize the side effects through drug formulation and the development of novel metallodrugs are ongoing (Oun et al., 2018).

Recent advancements in anti-cancer drugs other than platinum

The landscape of metal complexes in cancer therapy is continually evolving, fuelled by recent advancements and

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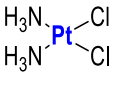
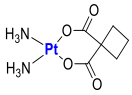
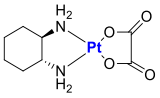
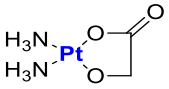
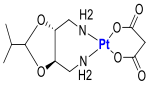
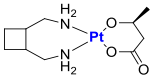
Table 1. Clinically approved platinum anti-cancer drugs.

	Cisplatin	Carboplatin	Oxaliplatin	Nedaplatin	Heptaplatin	Lobaplatin
Year of discovery	1965	1970	1976	1986	1990	1995
Year of approval and Market status	1979 Worldwide	1989 Worldwide	2002 Worldwide	1996 Japan	1999 Korea	2010 China
Clinical use	Lung, breast cancer, brain cancer, and ovarian.	Advanced ovarian cancer, lung, neck and head cancer.	Gastric and ovarian cancer, metastatic colorectal cancer.	Lung, bladder, ovary, and cervix cancer, neck and head cancer.	Gastric cancer.	Ovarian, lung, gastric, breast cancer, chronic myeloid leukaemia.
Chemical structure						

emerging trends that promise to revolutionize cancer treatment in the years to come (Gou et al., 2021). While Pt-based therapeutics have been a foundation for treating malignancies, researchers are exploring the potential of other metals, such as Au, Ru, Cu, Fe, Ag, and Ti, for their anti-cancer properties (Lazarevic et al., 2017). These alternative metal-based compounds offer diverse mechanisms of action and a reduced risk of cross-resistance, expanding the arsenal against cancer.

Gold-based compounds

In numerous cancer cells, Au-based compounds demonstrate remarkable antiproliferative properties, and the ligands attached to them are essential for their circulation *via* the bloodstream and passage through plasma membranes, in addition to arriving at their intended biological targets. These factors led to the widespread usage of ligands that were synthesized from biological components found in the body, for example, sugars, amino acid and peptide derivatives, and thiol-functionalized DNA bases.

Efficacy

Gold-based compounds, particularly gold nanoparticles, have shown promise in cancer therapy (Siddique et al., 2020). These nanoparticles can be functionalized with various biomolecules to improve their targeting of cancer cells. They are utilized in drug delivery, photothermal therapy, and imaging.

Ruthenium-based compounds

Ruthenium-based complexes have been considered because of their diverse coordination chemistry and cytotoxic properties. Compounds like NAMI-A and KP1019 have shown effectiveness in clinical trials to treat solid tumors (Alessio et al., 2019). New research is revealing Ru complexes' potential as anti-cancer agents.

Efficacy

Some have demonstrated a potential profile as an anti-cancer immune-modulating substance (Wernitznig et al., 2019), outstanding redox potential (Notaro et al., 2020), and strong topoisomerase inhibitor (Xiong et al., 2020). However, some have demonstrated promising outcomes, including suppression of tubulin production, antimetastatic action, and excellent selective nature for malignant cells (Qin et al., 2019; Subarkhan et al., 2019; Acharya et al., 2019; Soldevila-Barreda et al., 2020; Del Olmo et al., 2020).

Copper-based compounds

Many Cu complexes have been investigated for their reactivity towards cancer cells during the past 40 years, and many of them may be suitable as phase II and phase III drugs in cancer therapy. Furthermore, there is encouraging data supporting using ^{64}Cu in nanoparticles as radiopharmaceuticals for treating hypoxic tumors and performing positron emission tomography (PET) imaging. Still, only a small number of molecules have progressed beyond testing in animal models, and none of them has been approved as cancer chemotherapeutic drugs.

Efficacy

Copper complexes have demonstrated anti-cancer activity by inhibiting angiogenesis, an essential mechanism for the formation of tumors. Researchers are exploring the usage of Cu-based compounds as potent anti-neoplastic agents and angiogenesis inhibitors [Adhikari et al., 2019; Molinaro et al., 2020].

Iron-based compounds

The widespread activity observed for naturally occurring iron-bleomycin and ferrocenium salts, viz., ferrocenium picrate and trichloroacetate, sparked an early

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interest in the anti-cancer properties of Fe complexes. Their effectiveness was attributed to oxidative DNA damage caused by their disruption of oxidative equilibrium in cancer cells.

Efficacy

Iron-based complexes have been scanned for their potentiality in cancer therapy. Iron nanoparticles, for example, can be used in hyperthermia therapy, where they generate heat when exposed to magnetic fields, leading to localized cancer cell destruction (Norouzi et al., 2020).

Silver-based compounds

Due to their exceptional SERS/SPR, surface characteristics, morphological diversity, surface charge, dissolution rate, and controlled release of Ag ions to mediate antimicrobial toxicity in addition to their cytotoxic nature for cancer cells, as well as their effective biocompatibility, silver nanostructures have the potential to be used as antimicrobial, anti-cancer, and diagnostic agents.

Efficacy

Silver nanoparticles have shown possibilities in cancer therapy because of their exclusive traits, including their capacity to induce cell death in cancer cells (Miranda et al., 2022). They can also be utilized in targeted drug delivery and photothermal therapy.

Titanium-based compounds

Titanium-based compounds, such as titanium dioxide nanoparticles, have been analyzed for their potency in photodynamic therapy (PDT).

Efficacy

In PDT, these nanoparticles are activated by light, and thereby, reactive oxygen species are produced that can selectively kill cancer cells (Zhang et al., 2020). Furthermore, phototherapy for skin malignancies has been successfully implemented with UV-stimulated TiO_2, yet its use for the majority of deep-tissue tumors has resulted in unfavorable outcomes.

Other metal-based compounds, including Ni, Zn, and Pd-based complexes, are also under investigation for their potential in cancer treatment (Bhattacharjee et al., 2022; Adhikari et al., 2023). Their unique chemical properties make them attractive candidates for drug development.

New metal-based anti-cancer drugs under clinical trials

New platinum-based compounds

BBR 3464

BBR 3464 (Fig. 1) is a trinuclear platinum compound having two monofunctional [*trans*-$PtCl(NH_3)_2$]platinum units connected by a platinum tetra-amine unit [*trans*-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2]^{2+}$ that binds DNA by hydrogen bonding and electrostatic interactions (Manzotti et al., 2000). BBR 3464 has outstanding preclinical features. It exhibited activity in cisplatin-sensitive and cisplatin-resistant tumors, and is around four to eight times more powerful than cisplatin. In *p53* mutant tumors, BBR 3464 was also found to be more potent compared to cisplatin. BBR 3464 inhibits tumor growth for a longer period of time than cisplatin does, indicating that the capacity to disrupt the cell cycle may vary greatly. BBR 3464 is effective against cell lines showing cisplatin resistance and exhibits its cytotoxic effects at doses ten times lower than cisplatin (Sessa et al., 2000). BBR 3464 is more effective than therapeutic combinations of Pt complexes with taxanes, according to phase II investigations in persons with non-small cell lung carcinomas as well as ovarian tumors in advanced stages, but it is ineffective against gastric tumors (Hensing et al., 2006).

Satraplatin

Satraplatin (JM-216) (Fig. 1), also known as bis-(acetate)-ammine dichloro-(cyclohexylamine) platinum(IV), belongs to the mixed amine Pt(IV) dicarboxylate dichloride series (Kellandet al., 2000). Satraplatin, a fourth-generation Pt drug with efficacy toward cisplatin-resistant malignancies and a safety profile similar to carboplatin, was the first orally active Pt-based drug (Choy et al., 2008). The lipophilicity and stability of satraplatin were carefully considered so that it could be taken orally. A lot of studies have been done on satraplatin as a potent second-line chemotherapeutic agent for those with metastatic castration-resistant prostate cancer. It has demonstrated anti-cancer efficacy comparable to cisplatin and carboplatin in *in vitro* and *in vivo* investigations. It has also demonstrated anti-cancer properties in several *in-vitro* tumor models that are resistant to Pt (Sternberg et al., 2007).

Picoplatin

Picoplatin (Fig. 1), is diammine dichloro-(2-methylpiridine) platinum(II) (AMD473, JM473, ZD0473), a brand-new Pt-based drug developed to combat platinum resistance (Holford et al., 1998). It was initially developed to circumvent the detoxification of Pt by intracellular thiols, one of the recognized causes of Pt resistance, by adding a large methylpyridine to offer steric interference to direct interaction with Pt (Beale et al., 2003). Picoplatin has been shown to be effective against certain non-small cell lung carcinomas, mesothelioma, small cell lung cancer, and ovarian cancer that show resistance to cisplatin and oxaliplatin in preclinical investigations (Kelland et al., 2007).

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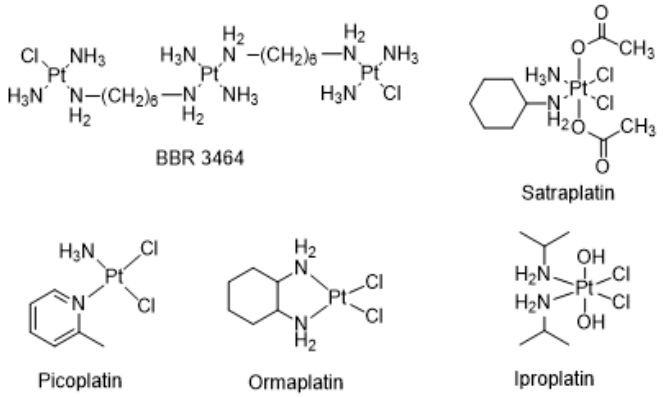

Figure 1. Platinum-based anti-cancer therapeutics under clinical trial.

nontoxic highest tolerated dosage could not be established (Johnstone et al., 2016).

Iproplatin

Dichloro-dihydroxy-bis(isopropylamine) platinum(IV) (iproplatin)(Fig. 1) is analogous to ormaplatin. It has two equatorial chlorides which are *cis* to one another. Iproplatin is less vulnerable than ormaplatin to reduction and inactivation by biological reducing agents since it has -OH ligands, facilitating less obstructed diffusion throughout the body (Johnstone et al., 2016).

New ruthenium-based compounds

The scientific community was inspired by the success of cisplatin in discovering new metal compounds with anti-cancer activity that are greater than Pt compounds, have reduced toxic reactions, or are active in various kinds of cancers. Complexes made of Ru are appear to be promising in this situation (Lee et al., 2020).

Table 2. Table representing a few of the examples of the Pt-based compounds under clinical trials.

Name of the Pt-based compounds	Types of cancer	Mechanism of action	References
BBR 3464	Non-small cell lung carcinomas as well as ovarian cancers in advanced stages.	DNA adducts formation, blocking DNA transcription in addition to replication, and ultimately causing apoptosis in cells.	Manzotti et al., 2000; Hensing et al., 2006
Satraplatin	Potent second-line anti-cancer agent for those having metastatic castration-resistant prostate cancer.	DNA adducts formation, intra and interstrand crosslinks, and DNA template deformation occur when cells slow down during the S stage and then arrest in the G2 stage.	Mellish et al., 1995; O'Neill et al, 1999
Picoplatin	Non-small cell lung carcinomas, small cell lung tumor, mesothelioma, and ovarian malignancy that show resistance to cisplatin and oxaliplatin.	Apoptotic cell death by DNA binding interferes with DNA replication and transcription.	Kelland et al., 2007
Ormaplatin	Potent anti-cancer drug towards cisplatin-resistant human ovarian cancer cell lines.	Cancer cells undergo apoptosis due to immunological reactions, DNA lesions, RNA synthesis inhibition, and inhibition of DNA synthesis.	Johnstone et al., 2016
Iproplatin	Especially used to treat cisplatin-resistant ovarian cancer cell lines.	Formation of Pt-DNA adducts and DNA crosslinks, which hinder DNA replication and cause cell death.	Johnstone et al., 2016

Ormaplatin

A Pt analogue called ormaplatin (Fig. 1) is tetrachloro (1,2-diaminocyclohexane) platinum (IV), which was developed due to a changed toxicity profile and non-cross resistance to cisplatin. Ormaplatin is comparable to oxaliplatin since it contains 1,2-diaminocyclohexane carrier ligand and causes dose-limiting neurotoxicity. On the highest tolerated dosage, ormaplatin was seen to cause severe neurotoxicity, and in certain instances, a

NAMI-A and KP1019/1339

NAMI-A ((ImH)[*trans*-$RuCl_4$(dmso-S)(Im)], Im = imidazole) and KP1019/1339 (KP1019 = (IndH)[*trans*-$RuCl_4(Ind)_2$], Ind = indazole; KP1339 = Na[*trans*-

$RuCl_4(Ind)_2$]) (Fig. 2) are two structurally correlated Ru(III) complexes, which have fascinated a major consideration in the pharmaceutical chemistry as auspicious antiproliferative drugs. With two axial indazole ligands and four equatorial chloride ligands, the geometry of the Ru(III) in KP1019 is comparable to NAMI-A. In comparison to NAMI-A, KP1019 is substantially more stable in the solid state and has reasonable solubility in water. In physiological environments, both Ru derivatives are not particularly stable; NAMI-A is much less stable than KP1019. Given their limited stability in physiological settings, it is possible to categorize both Ru medications as prodrugs straightaway. NAMI-A has been shown to have a suppressive impact towards the development of cancerous metastases in the case of a diversity of animal tumor models, but it has not been shown to have straightforward cytotoxicity on primary tumors. In contrast, KP1019 has anti-malignancy action towards several primary tumors in humans by cytotoxic apoptotic induction (Alessio et al., 2019). Both compounds have been studied in clinical studies that have yielded minimal indication of systemic toxicity. Even if they don't seem to have much of an anti-cancer effect when used alone, there is still an opportunity to investigate more cancer models and employ these substances in combination therapy.

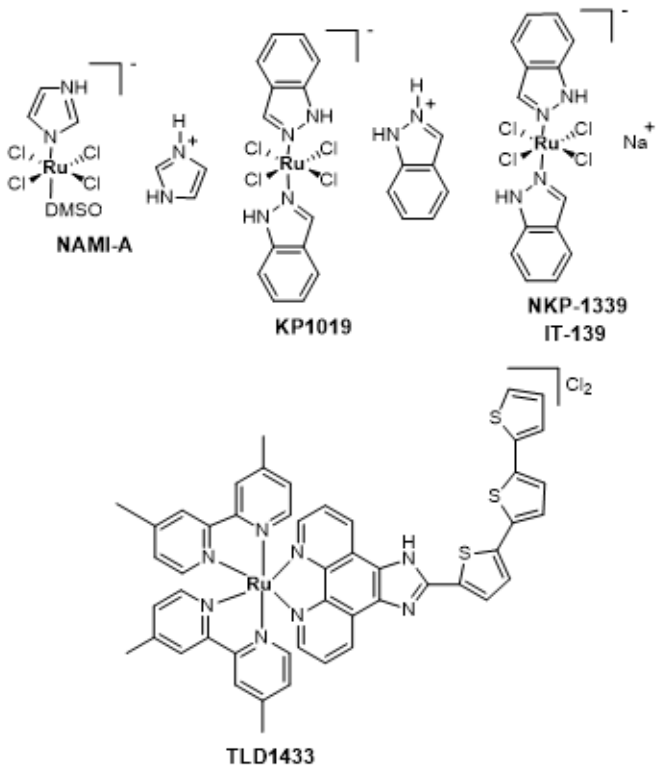

Figure 2. Ru-based anti-cancer drugs under clinical trial.

New copper-based compounds

Although Cu complexes have a significant level of toxicity, preclinical and clinical investigations have provided encouraging data to support this potential (Santini et al., 2014). Few of these compounds have entered the clinical trial stage as a result of the encouraging outcomes from *in vivo* experiments.

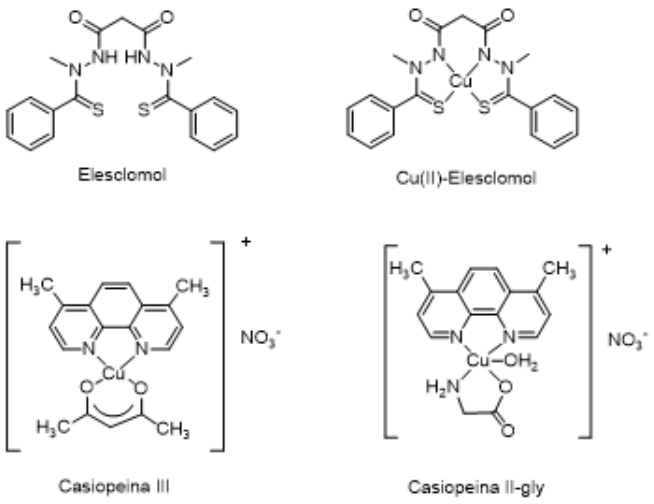

Figure 3. Copper-based anti-cancer drugs under clinical trial

Elesclomol

Elesclomol (Fig. 3), is an anti-cancer therapeutic that targets mitochondrial metabolism. Elesclomol was previously known to cause oxidative stress; however, it has since been discovered that it also suppresses cancer by causing cuproptosis. Elesclomol and Cu(II)-elesclomol are both extremely active *in vitro* and often suppress the development of tumor cells at low concentrations (nanomolar). Elesclomol significantly increased the effectiveness of chemotherapy drugs like paclitaxel in human tumor xenograft models and demonstrated antiproliferative action for an extensive array of malignant cell types. Elesclomol was well tolerated in phase I clinical testing when used in conjunction with paclitaxel in those with resistant solid tumors, and its toxicity profile was comparable to that of paclitaxel used as a single drug (Berkenblit et al., 2007).

Casiopeinas: Casiopeina III and Casiopeina II-gly

Casiopeinas are a class of copper-based complexes that revealed in vitro as well as in vivo evidence of cytotoxic natures, genotoxicity, antiproliferative, and antineoplastic activities (Silva-Platas et al., 2016). Casiopeinas are mixed Cu derivatives of Cu(II) with 4,7-dimethyl-1,10-phenanthroline and glycocol (CasII-gly) or with 4,7-dimethyl-1,10-phenanthroline and acetylacetone (CasIII) (Fig. 3) (Serment-Guerrero et al., 2017). CasII-gly has an anti-cancer impact by preventing the cell cycle, controlling fibroblast transformation, or

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minimizing the phenomenon of tumor cells migrating out of control. Phase I clinical trials for CasII-gly are being conducted to evaluate its toxic effect in humans. Experiments revealed that it slows energy metabolism and has significant cardiotoxicity, which will likely result in the termination of the clinical trials. One of the phase I clinical trials involving CasIII investigated its potential for colon cancer and acute myeloid leukaemia (Vertiz et al., 2014). To treat cervical cancer, CasII-gly was tested in clinical settings because it prevents HeLa cells from migrating and proliferating.

minimize side effects. Nanoparticle formulations of metal-based drugs are being developed to improve drug delivery and increase tumor targeting. These nanoparticles can enhance drug stability, reduce side effects, and increase drug accumulation in cancer cells. Scientists are exploring new metal-based derivatives that have distinctive mechanisms of action to overcome resistance as well as improve selectivity for cancer cells. These compounds may offer new treatment options.

The development of Pt-based anti-tumor therapeutics,

Table 3. Table representing a few of the examples of the Ru-based compounds under clinical trials.

Name of the Ru-based compounds	Types of cancer	Mechanism of action	References
NAMI-A	Effective againstlung metastases, non-small cell lung carcinoma	Reduction in the movement of invasive tumor cells due to interactions with extracellular matrix collagens and actin-type proteins on the cell surface	Gava et al., 2006; Sava et al., 2004
KP1019/1339	*Effective against* colorectal carcinoma cells (SW480 and HT29)	Generates ROS, damages DNA, which stops the cell cycle, triggers the mitogen-activated protein kinase signaling pathway, modifies intracellular lipid and metal balance, and impacts chromatin assembly.	Alessio et al., 2019

Table 4. Table representing a few of the examples of the Cu-based compounds under clinical trials.

Name of the Cu-based compounds	Types of cancer	Mechanism of action	References
Elesclomol	Advanced-stage melanomas, non-small cell lung malignancy, and soft tissue sarcoma.	Elesclomol prompts oxidative stress by ROS generation within cancer cells.	Kirshner et al., 2008; Zheng et al., 2022
Casiopeinas	CasIII effective against colon cancer and acute myeloid leukaemia. CasII-glyeffective against HeLa cell.	Intercalate into the DNA and subsequently inhibit its replication, in addition to biochemical mechanisms that lead to apoptotic cell death.	Silva-Platas et al., 2016; Serment-Guerrero et al., 2017; Vertiz et. al., 2014

Future perspective and conclusion

The future of metal-based anti-cancer drugs is promising. Research efforts are focused on improving their effectiveness, reducing side effects, and expanding their applicability through innovative approaches. Metal-based drugs are increasingly being used in combination with targeted therapies, immunotherapies, and other chemotherapy agents. These multidimensional approaches aim to enhance treatment outcomes and

from the accidental discovery of cisplatin to the modern era of metallodrugs, represents a remarkable journey in the history of oncology. These drugs have saved countless lives and continue to be integral components of cancer treatment regimens. As research and innovation progress, metal-based drugs will remain pivotal in the fight against cancer, evolving to meet the challenges posed by this relentless disease. With ongoing efforts to enhance their effectiveness and reduce their after effects,

the future of metallodrugs shines ever brighter, offering hope to patients.

The journey of metal-based drugs in cancer therapy, from their ancient roots to the forefront of modern medicine, is a testament to human ingenuity and the relentless pursuit of innovative solutions to one of the most challenging diseases known to humanity. The principles governing their design, the historical significance of metals in medicine, and the promising trends in recent years all point to a shining future where metal-based drugs continue to illuminate the path towards effective cancer treatments.

The prospects of metallodrugs in cancer therapy shine brightly with promise and potential. Metal-based compounds have diverse applications in cancer therapy, ranging from established Pt-based drugs like cisplatin to emerging therapies involving Au nanoparticles, Ru-based complexes, and more. These compounds offer a wide range of mechanisms to target and disrupt cancer cells, and ongoing research continues to uncover their complete potential in combating cancer. As our understanding of these compounds deepens and innovative approaches are developed, metal-based cancer therapies are probably to perform a progressively more significant part in the field of oncology.

As we look ahead, the landscape of metal-based drugs in cancer therapy continues to evolve. Innovations in drug design and combinatorial therapies are reshaping the way we approach cancer treatment. Novel metal-based compounds and advanced delivery systems offer exciting possibilities for increasing efficacy while minimizing side effects. Additionally, integrating metal-based agents into cancer imaging and diagnosis further enhances the ability to detect and monitor tumors.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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