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REVIEW ARTICLE

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Cisplatin — properties and clinical application

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ABSTRACT

Chemotherapy is one of the basic methods of cancer treatment, which uses compounds with a broad spectrum of activity. Among the diverse group of cytostatic drugs, platinum derivatives play an important role in cancer therapy, including cisplatin. Cisplatin is a first generation platinum drug approved in medicine in the 1980s. The mechanism of the anti-tumor activity of cisplatin is based on pro-apoptotic and antiproliferative activity. Cisplatin, through the formation of appropriate adducts with DNA, damages the structure of the molecule. Currently, cisplatin is used in the treatment of numerous malignant neoplasms. Despite the high therapeutic efficacy, the drug has many side effects, which may include, among others: ototoxicity, cardiotoxicity, neurotoxicity, hepatotoxicity and nephrotoxicity. A significant problem in cisplatin therapy is also the development of resistance of cancer cells to the action of this drug. The mechanism of cell platinum resistance is diverse and depends on many factors. Organ toxicity and the development of resistance induced by cisplatin may limit the pharmacological dose of the drug and its therapeutic efficacy. Therefore, studies are still being conducted to assess the therapeutic effect of the combined interaction of cisplatin with other chemotherapeutic agents and compounds with anticancer potential.

Key words: cancer, chemotherapy, cisplatin, platinum resistance, toxicity, multi-drug therapy

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Introduction

Neoplastic diseases are still a serious health problem in the modern world. The main methods of fighting cancer are radiation therapy, immunotherapy, and hormone therapy. A common and frequently used method in the treatment of many types of cancer is chemotherapy, which provides the use of drugs with a broad effect. Drugs used in cancer chemotherapy constitute a diverse group of compounds. They include, among others, topoisomerase inhibitors (camptothecin derivatives, anthracyclines), microtubule stabilizers (taxanes, vinca alkaloids), antimetabolites (gemcitabine, methotrexate, 5-fluorouracil), and alkylating drugs (cyclophosphamide, ifosfamide) [1]. Chemotherapeutic agents containing metal atoms also play an important role in the treatment of cancer. The group of alkylating drugs includes platinum compounds, such as cisplatin, carboplatin, and oxaliplatin [1]. Currently, cisplatin is a platinum complex widely used in oncological therapy. Despite its high efficiency, this compound is highly toxic. Therefore, efforts are still made to develop new therapies based on using cisplatin in combination with other compounds with anti-cancer potential. Multi-drug treatment of neoplastic cells may increase therapeutic efficacy.

The issue of the mechanisms of the formation, growth, and treatment of neoplastic diseases is still discussed in numerous scientific papers. This study aims to present the mechanisms of the cellular interaction of cisplatin, the development of cellular resistance, the range of side effects, and new possibilities for using cisplatin in anticancer therapy.

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Cisplatin

Historical overview

Cisplatin [cis-dichlorodiammine platinum (II)] is a first-generation platinum drug containing two chloride ligands in the *cis* configuration [2]. This compound was synthesized in 1845 by A. Werner, who 48 years later described the chemical structure of cisplatin. In the 1960s, a research team led by B. Rosenberg observed that cisplatin is formed as a result of the electrolysis of platinum electrodes [3]. By analyzing the effect of the electromagnetic field on bacterial cells, Rosenberg and his colleagues found that cisplatin inhibits the proliferation of bacterial cells [3, 4]. Therefore, there were indications that this compound may show an inhibitory effect on other cells, including cancer [3]. The antiproliferative effect of cisplatin on cancer cells was confirmed in an experimental mouse model [3, 5], which resulted in the implementation of cisplatin in subsequent research stages. Based on the results obtained, in 1978 cisplatin was approved as an anti-cancer drug [6]. However, studies were still conducted to assess the effectiveness of this drug in various types of cancer cells [7, 8].

Transport and biotransformation

The structure of cisplatin in the blood, due to the high concentration of chloride ions (approx. 100 mM), shows great stabilization [4]. This compound undergoes biological changes only after the drug is absorbed into the cell [9]. The process of cisplatin transport into cells has not been fully elucidated. Literature data show that cisplatin can penetrate the plasma membrane by passive diffusion [10, 11]. There are also reports that the partial uptake of cisplatin may be mediated by protein transporters [11]. Copper transporters (Ctr1, Ctr2), ATPase (ATP7A, ATP7B), organic cation transporters (OCT-2), and multidrug and toxin extrusion proteins (MATE 1) are probably associated with the transport of cisplatin through cytoplasmic membranes [11, 12]. Membrane transporters involved in the uptake and accumulation of cisplatin in cancer cells are responsible both for the effectiveness of the drug and the development of side effects [10]. Transport of cisplatin to cells can also take place with the participation of the sodium-potassium pump (Na^+/K^+-ATPase) [4].

Cisplatin is hydrolyzed inside the cell [4]. This process is regulated by the appropriate concentration of chloride ions. The reduced level of Cl^- ions in the intracellular environment (approx. 4-12 mM) accelerates the hydrolysis of cisplatin [9]. It has been shown that the positively charged molecules formed by hydrolysis ($cis\text{-}[Pt(NH_3)_2Cl_2(OH_2)]^+$/$cis\text{-}[Pt(NH_3)_2Cl_2(OH_2)_2]^{2+}$) are characterized by a higher biological activity than the neutral forms of the complex [13]. Therefore, it is believed that it is the secondary metabolite of cisplatin [cis-diaminadihydroxyplatin (II)] that exhibits strong pharmacotherapeutic properties [14].

The mechanism of antitumor action

Literature data show that the mechanism of the anti-cancer effect of cisplatin is based on the direct effect of the drug on the DNA structure. The basis of cisplatin's action is the creation of cross-links in the DNA structure between platinum (II) and two adjacent guanine molecules [15]. According to the literature, the most commonly observed is the attachment of cisplatin to the N7 atoms of guanine [9]. Presumably, the Pt-N7 guanine bonds formed in this way show high stability and thus determine the cytotoxic effect of the compound on cancer cells [16]. Cisplatin can cross-link with base pairs within a single strand or between a DNA double helix, resulting in the formation of monoadducts or diadducts (double adducts). The type of Pt-DNA adducts formed may exert a significant influence on the biological activity of the drug. It was found that the genotoxic effect of cisplatin results from the formation of monoadducts, while the formation of double adducts — inside or between strands — results in the cytotoxic properties of the compound [17]. Nevertheless, the resulting adducts lead to a disturbance of the spatial structure of DNA, which results in inhibition of acid replication and transcription [2, 9, 14, 18]. Under normal conditions, repair systems are involved in the repair of DNA damage, including Nucleotide Excision Repair excision repair (NER), homologous recombination (HR), and mismatch repair Mismatch Repair System (MMR) [4, 19]. In neoplastic cells, depending on their sensitivity and the concentration of cisplatin used, the mechanisms of the repair process are disrupted, which results in the induction of apoptotic death signals. Depending on the type of DNA damage caused by cisplatin, in tumor cells, Ataxia Telangiectasia Rad 3-Related (ATR) and Mitogen-Activated Protein Kinases (MAPK) are activated, which stimulate p53 proteins in the further pathway of the cellular response [20]. Moreover, independent of the phosphorylation of the ATR kinases, the action of cisplatin triggers the expression of the p73 nuclear protein in the cells. The accumulation of p73 is related to cisplatin-activated oncogenic tyrosine kinase c-Abl. The increased reactivity of the p53 and p73 proteins leads to the activation of further mechanisms involved in the induction of the apoptosis process [18]. Cisplatin affects the internal pathway of apoptotic death by stimulating the pro-apoptotic protein Bax, changing the permeability of the mitochondrial membrane, releasing cytochrome c, and activating the caspase cascade [18]. Permeabilization of the mitochondrial membrane caused by cisplatin may also result from the drug's influence on the production of free oxygen radicals (ROS) [21, 22].

The literature shows that cisplatin, depending on its concentration, can also induce necrotic cell death [23]. Research results indicate that pronecrotic cisplatin concentrations first activate the mechanisms of apoptotic death, which can be blocked at the level of effector caspases. Inhibition of caspase activity consequently causes cell necrosis [23, 24]. Mediators of cisplatin-induced necrotic death may also be calpains, TNF-α cytokines, and poly (ADP-ribose)-1 (PARP1) polymerase — factors related to the mechanism of nephrotoxic action of the drug [24, 25].

The antitumor properties of cisplatin are also demonstrated by its antiproliferative activity. The complex has been shown to exert a strong influence on the checkpoints of the cell cycle. In response to DNA damage, the cell is initially arrested in the S phase. However, further action of cisplatin leads to an inhibition of cyclin Cdc2 A activity, which ultimately results in cell division arrest in the G2/M phase [18, 20]. Ataxia Telangiectasia Mutated (ATM) kinases, activated by the action of cisplatin, are also involved in the inhibition of cell division [20].

Mechanisms of cell resistance

The response of cancer cells to the cytostatic drugs has a significant impact on the effectiveness of chemotherapeutic treatment. In cancer therapy, the development of cellular resistance is a frequently observed phenomenon [5]. Drug resistance occurs when cancer cells fail to undergo apoptosis at a clinically specified dose [26]. The platinum resistance that hinders the treatment of neoplasms may have features of both innate and acquired resistance [27]. According to the literature, the mechanisms involved in platinum resistance vary and may be caused by: (1) decreased drug absorption resulting in reduced intracellular accumulation, (2) increased inactivation of cisplatin, (3) impaired drug transport into cells, (4) accelerated removal of the drug from cells (efflux), (5) intensified repair of the resulting DNA damage, mainly associated with the activation of NER repair systems [4, 13, 18, 19, 20, 26]. The disturbed signal of apoptotic death also has a significant influence on the development of cellular resistance. Cancer cells with p53 dysfunction acquire resistance through disrupted mechanisms of the apoptotic pathway [27]. A similar effect is also shown by the overexpression of apoptosis inhibitors, e.g. survivin and factor X-linked Inhibitor of Apoptosis Protein (XIAP), which increase platinum resistance by lowering the activity of caspases [26]. Weakened cisplatin transport to neoplastic cells during chemotherapeutic treatment may be caused by functional changes in plasma membranes and membrane transporters [27]. It is believed that overexpression of CTR1 transporters increases the sensitivity of cancer cells to cisplatin, enhancing its cytotoxic activity [16]. Their impaired functioning may, therefore, play an important role in the development of cell resistance to cisplatin treatment. The protein transporters ATP7A and ATP7B are also involved in the formation of cellular resistance. Increased ATP7A expression is responsible for the decreased effect of cisplatin in cancer cells while ATP7B overexpression results in accelerated drug outflow from cells [11].

According to the literature, platinum resistance may be associated with the overexpression of glutathione transferase (GSTs) [28]. The enzyme is associated with the drug detoxification process, which leads to inactivation of cisplatin and reduced treatment effectiveness [14, 28]. Therefore, the use of GSTs inhibitors (e.g. ethacrynic acid) may increase the accumulation of cisplatin in platinum-resistant cells and significantly improve the therapeutic effect [28]. The intracellular concentration of glutathione (GSH) is also associated with the platinum resistance mechanism. Until recently, the role of GSH in the development of cellular resistance to cisplatin was ambiguous [4]. It is now known that high GSH levels may promote cellular resistance [29]. Metallothioneins (MT) act in a similar way, and by capturing cisplatin, they reduce the sensitivity of cells to the drug [14, 30]. The greatest importance in the resistance mechanisms is attributed to the metallothioneins MT1 and MT2 [4, 31] although the participation of other proteins from the MT group is also possible. As reported in the literature, cisplatin binds to cysteine-rich proteins, therefore, high concentrations of glutathione and metallothioneins in neoplastic cells may favor the development of acquired resistance [32].

The development of cellular resistance to cisplatin may also result from the overexpression of cyclooxygenase (COX) [33–35], characteristic of many types of malignant tumors, e.g. cancer of the esophagus, bladder, cervix and ovary [30]. It was shown that the applied COX-2 inhibitors, by inhibiting the expression of the anti-apoptotic protein Bcl-2, can effectively increase the pharmacological activity of cisplatin [30]. The COX inhibitors include e.g. non-steroidal anti-inflammatory drugs [36]. Cisplatin conjugates with COX-1, and COX-2 inhibitors (e.g. indomethacin and ibuprofen) accelerate drug transport into cells, increase cytotoxic activity, and inhibit the development of drug resistance [33]. It has been observed that celecoxib may also have a similar effect in osteosarcoma [36] and ovary cells [35], and NS-398 in non-small cell lung cancer [34]. These compounds enhance the anti-cancer effect of cisplatin and, depending on the PI3K/Akt signaling pathway, induce the apoptotic death process [34, 36]. The importance of COX in reducing drug resistance of cancer cells is poorly understood. Currently, the role of COX inhibitors does not affect routine clinical practice. However,

the results obtained so far suggest that the use of COX inhibitors may become the direction of further research as a new strategy in cancer treatment. It is possible that the combination of cisplatin with COX inhibitors may in the future contribute to the improvement of the effectiveness of the anti-cancer therapies [37].

In addition to biochemical and molecular factors, environmental factors also play an important role in the resistance of cancer cells to cisplatin, e.g. pH value. Cisplatin activity has been observed to be greatest at acidic pH. Increased pH reduces the binding of cisplatin with DNA, inhibits the formation of Pt-DNA adducts, and thus weakens the pharmacological effect of the drug [30]. The mechanisms responsible for the development of resistance of cancer cells to cisplatin are diverse [20]. This is a key research issue in overcoming platinum resistance by cancer cells.

Toxicity

Cisplatin is used in the treatment of various types of cancer, including cancer of the head and neck, lung, testes, prostate, ovaries, bladder, cervix, esophagus, breast, and stomach [12, 38, 39]. The use of cisplatin and its effectiveness in cancer therapy may be limited due to numerous side effects. The frequency of side effects depends on the used cisplatin dose, including the cumulative dose (Tab. 1). Literature data report that some compounds have a protective effect against cisplatin-induced toxicity. Currently, these compounds are not routinely used in conjunction with anti-cancer therapy. However, studies are still being conducted to assess the protective potential of some of these compounds, therefore, they may find wider applications in the future.

Ototoxicity

Changes in the hearing system may appear early in the treatment with cisplatin [40]. Hearing impairment caused by the action of cisplatin depends on the dose and duration of drug action, as well as the patient's age [41], and is more often observed in children than adults [40, 41]. Ototoxic disorders can manifest as earache and tinnitus, leading to partial hearing loss. Initially in the high-frequency range of sounds [40], then also including lower tones [42], including persistent and bilateral ototoxicity [40]. The mechanisms underlying the development of cisplatin-induced ototoxicity remain unclear. It is assumed that a key role in the pathogenesis of ototoxicity may be played by a disturbed antioxidant system, development of inflammatory processes, induction of apoptosis, and cellular autophagy [42]. The use of protective agents may limit the ototoxic effects of cisplatin [41, 43]. Among them, great hope is raised, by N-acetylcysteine, D-methionine, ebselen, amifostine, dexamethasone, and flunarizine [43]. In clinical trials, the evaluation of the otoprotective effect of sodium thiosulfate (Identifier: NCT04541355, Phase II; Identifier: NCT04262336, Phase I) and N-acetylcysteine (Identifier: NCT04291209, Phase I and II; Identifier: NCT02094625, Phase I) was implemented.

Cardiotoxicity

Disorders in the proper functioning of the cardiovascular system caused by cisplatin can be diverse and include, among others, myocardial fibrosis and inflammation, heart failure, hypertension, arrhythmia [44]. There are reports in the literature describing cases in which patients developed cardiac dysfunction or even myocardial infarction after treatment with cisplatin [45].

Table 1. The incidence of cisplatin-induced toxicity

Cisplatin-induced toxicity	Frequency of appearance
Ototoxicity	Hearing loss: 31% [102]
	Hearing impairment: 10–15% [102]
	Otological complaints during cisplatin treatment: 24% [103]
	Otological complaints following cisplatin treatment: 34% [103]
Cardiotoxicity	Bradycardia, tachycardia: often (≥ 1/100 to < 1/10 of patients) [102]
	Hypertension, myocardial infarction: rarely (≥ 1/10000 to < 1/1000 of patients) [102]
Neurotoxicity	Peripheral neuropathy: often (≥ 1/100 to < 1/10 of patients) [102]
	Brain dysfunction: rarely (≥ 1/10000 to < 1/1000 of patients) [102]
Hepatotoxicity	Liver dysfunction, elevated levels of aminotransferase: often (≥ 1/100 to < 1/10 of patients) [102]
	Reduced albumin levels in the blood: rarely (≥ 1/10000 to < 1/1000 of patients) [102]
Nephrotoxicity	Acute kidney injury: very often (≥ 1/10 of patients) [102]
	20–30% [39]
	28–42% [104]
	32% [105]

Cisplatin-induced cardiovascular disorders most often limit the continuation of chemotherapy [44]. The effect of cisplatin on cardiotoxicity remains unclear. Presumably, electrolyte imbalances, including hypomagnesemia caused by the action of cisplatin, may play a significant role in the development of cardiological changes [45]. Early diagnosis of cardiotoxicity can prevent permanent complications of the cardiac system [45]. Literature data report the cardioprotective effect of some agents against cisplatin-induced changes in animals, e.g. ginger [44], thymoquinone [46], green tea, vitamin E [47], acetyl L-carnitine [48].

Neurotoxicity

The development of the neurotoxic effect of cisplatin is determined by the accumulation of the drug in the dorsal root ganglia, which may affect the proper functioning of sensory neurons [49] and the development of peripheral neuropathy [50]. The changes in the nervous system may be permanent and may limit the range of therapeutic doses [50, 51]. Often, adverse effects of cisplatin on the nervous system may not appear until after chemotherapy has been completed [50]. The mechanism of the neurotoxic effect of cisplatin may be related to oxidative damage, mitochondrial dysfunction, inhibition of proliferation, and induction of apoptosis of neuronal cells [51, 52]. It has been shown that the neuroprotective factors in relation to changes induced by cisplatin include, *inter alia*, glutathione and vitamin E [53]. In experimental animal models, it has been observed that cisplatin-induced neurotoxicity can also be reduced by routin, which, by enhancing the antioxidant system, has a protective effect on brain tissue [51]. Literature data show that concerning cisplatin activity, neuroprotective effects are also shown by oxytocin [54], sitagliptin [55], mesna [56], sodium selenite [57], and the Ginkgo Biloba extract [52].

Hepatotoxicity

Literature data show that cisplatin causes an increase in biochemical indicators and changes in the structure of hepatocytes. Cisplatin-induced hepatotoxicity may result from increased drug accumulation in liver cells [58]. Although the mechanism of the toxic effect of cisplatin on the liver has not been fully understood, it is assumed that the development of hepatotoxicity is a result of increased oxidative stress [58, 59]. It has been observed in studies *in vitro* and *in vivo* that the hepatotoxic effect of cisplatin may be enhanced by elevated levels of cytochrome P 450 2E1 [59]. Mitochondrial disorders, increased lipid peroxidation, abnormal Ca^{2+} homeostasis, and increased expression of the pro-inflammatory factor COX-2 are the basic aspects of the adverse effect of cisplatin on the liver [58]. According to the literature data, the hepatotoxic effect of cisplatin can be minimized by using compounds with antioxidant activity [60–65] or anti-apoptotic [65]. It has been shown that liver damage caused by cisplatin can be alleviated by, among others, dexpanthenol [60], hyperin [61], licorice extract [62], propofol [63], curcumin, vitamin E [64], and vinpocetine [65].

Nephrotoxicity

The nephrotoxic effect of cisplatin is a significant clinical problem. It can develop in approximately 30% of patients treated with cisplatin [39, 66]. Most often it manifests itself in acute kidney damage. The development of nephrotoxicity is closely correlated with the dose and frequency of drug administration [39] and thus with the degree of cisplatin accumulation in renal tubular cells [67]. OCT2 protein transporters play an important role in the development of the nephrotoxic effect of cisplatin, increasing the drug uptake in kidney cells [67]. According to the literature, cisplatin may disturb renal vascularization and lead to damage to the proximal tubules, mainly due to the induction of oxidative stress and overexpression of pro-inflammatory factors [67]. In the pathomechanism of renal cell damage, an important role is also played by signaling pathways responsible for the processes of apoptotic and necrotic death, as well as autophagy and the cell cycle [66–68]. Regulation of these factors may both limit the nephrotoxicity of cisplatin and reduce its therapeutic potential [12]. Therefore, the search for new compounds with a protective effect against the nephrotoxic effect of cisplatin is still ongoing. It has been observed that gelsemin [38], cilastatin [69], saponins isolated from the leaves of *Panax quinquefolius* [70], quercetin [68], eriocitrin [71], and mannitol [72], among others, may show the nephroprotective effect. Phase II and III clinical trials are still ongoing to evaluate the protective effects of pantoprazole and rosuvastatin against cisplatin-induced nephrotoxicity (Identifier: NCT04217512, NCT04817904) [73].

The use of cisplatin in multi-drug therapy

Cisplatin is used both as monotherapy and in combination therapy. The effectiveness of new cisplatin-based treatment regimens is still the subject of numerous clinical trials. These studies aim to compare the therapeutic efficacy of cisplatin in multi-drug systems in different types of cancer (Tab. 2) [73].

Lung cancer

Cisplatin-based chemotherapy has become a breakthrough in the treatment of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This chemotherapy is most effective in adjuvant and first-line treatment of NSCLC. It is also recommended to use two-drug systems with cisplatin and third-generation drugs. The standard chemothera-

Table 2. Sample clinical trials for the assessment of the effects of cisplatin in multi-drug therapy for selected malignant neoplasms (current status as of January 2022) [73]

Cancer	Combination Therapy	Drug (dose)	Clinical Trials Phase	Clinical Trials Identifier
Non-Small Cell Lung Cancer (NSCLC)	Cisplatin/Camrelizumab/ Paclitaxel	Cisplatin (75 mg/m^2), Camrelizumab (200 mg), Paclitaxel (130 mg/m^2)	II	NCT04338620$^{(R)}$
	Cisplatin/Gemcitabine	Cisplatin (60 mg), Gemcitabine (200 mg)	I	NCT02889666$^{(R)}$
	Cisplatin/Pemetrexed	Cisplatin (75 mg/m^2), Pemetrexed (500 mg/m^2)	III	NCT02743923$^{(ANR)}$
	Cisplatin/Pemetrexed	Cisplatin (75 mg/m^2), Pemetrexed (500 mg/m^2)	III	NCT02657434$^{(ANR)}$
	Cisplatin/Pemetrexed/Atezolizumab	Cisplatin (75 mg/m^2), Pemetrexed (500 mg/m^2), Atezolizumab (1200 mg)	III	NCT02657434$^{(ANR)}$
	Cisplatin/Etoposide	Cisplatin (80 mg/m^2), Etoposide (100 mg/m^2)	III	NCT02875457$^{(NR)}$
	Cisplatin/Etoposide/Apatinib	Cisplatin (80 mg/m^2), Etoposide(100 mg/m^2) Apatinib (250 mg/d)	III	NCT02875457$^{(NR)}$
Triple-Negative Breast Cancer (TNBC)	Nab-paclitaxel/Cisplatin/ /Carilizumab	Nab-Paclitaxel (125 mg/m^2), Cisplatin (75 mg/m^2), Carilizumab (200 mg)	II	NCT04537286$^{(R)}$
	Gemcitabine/Cisplatin	Gemcitabine (1250 mg/m^2), Cisplatin (75 mg/m^2)	II	NCT04297267$^{(R)}$
	Eribulin/Cisplatin *vs.* Gemcitabine/Cisplatin	Eribulin (1.4 mg/m^2), Cisplatin (75 mg/m^2) *vs.* Gemcitabine (1250 mg/m^2), Cisplatin (75 mg/m^2)	II	NCT04517292$^{(NR)}$
	Chidamine/Cisplatin	Chidamine (20 mg), Cisplatin (75 mg/m^2)	II	NCT04192903$^{(NR)}$
	Docetaxel/Cisplatin	Docetaxel (75 mg/m^2), Cisplatin (25 mg/m^2)	II	NCT04664972$^{(R)}$
Ovarian Cancer	Mitomycin C/Cisplatin	Mitomycin C (10 mg/m^2), Cisplatin (100 mg/m^2)	Not Applicable	NCT04747717$^{(R)}$
	Nab-paclitaxel/ Cisplatin/ /Sintilimab	Nab-paclitaxel (180-220 mg/m^2), Cisplatin (60-80 mg/m^2),Sintilimab (200 mg)	I/II	NCT03989336$^{(R)}$
	Manganese Chloride/Nab--paclitaxel/Cisplatin/Sintilimab	Manganese Chloride (0,4 mg/kg — inhalation), Nab-paclitaxel (180-220 mg/m^2), Cisplatin (60-80 mg/m^2), Sintilimab (200 mg)	I/II	NCT03989336$^{(R)}$
Bladder Cancer	Radiotherapy/Cisplatin	Radiotherapy (to 63 Gy), Cisplatin (20 mg/m^2)	Not Applicable	NCT01495676$^{(ANR)}$
	Radiotherapy/Cisplatin/ Gemcitabine	Radiotherapy (to 63 Gy), Cisplatin (20 mg/m^2), Gemcitabine (25 mg/m^2)	Not Applicable	NCT01495676$^{(ANR)}$
	Atezolizumab/Gemcitabine/ Cisplatin	Atezolizumab (1200 mg/m^2), Gemcitabine (1000 mg/m^2), Cisplatin (70 mg/m^2)	II	NCT03093922$^{(ANR)}$
	Etoposide/Cisplatin	Etoposide (100 mg/m^2), Cisplatin (80 mg/m^2)	II/III	NCT03992911$^{(R)}$
	Pembrolizumab/Cisplatin/ Gemcitabine	Pemrolizumab (200 mg), Cisplatin (35 mg/m^2), Gemcitabine (1000 mg/m^2)	II	NCT02690558$^{(ANR)}$
	Cabazitaxel/Cisplatin	Cabazitaxel (15 mg/m^2), Cisplatin (70 mg/m^2)	II	NCT01616875$^{(ANR)}$
Head and Neck Cancer	Cambrelizumab/Radiotherapy/ /Cisplatin	Cambrelizumab, Radiotherapy (66–70 Gy), Cisplatin (75–100 mg/m^2)	II	NCT04405154$^{(NR)}$
	Cambrelizumab/ /Cisplatin/Nab-paclitaxel	Cambrelizumab (200 mg), Cisplatin (60 mg/m^2), Nab-paclitaxel (260 mg/m^2)	II	NCT04826679$^{(R)}$
	Radiotherapy/Pembrolizumab/ /ISA101b/ Cisplatin	Radiotherapy (70 Gy), Pembrolizumab (200 mg), ISA101b, Cisplatin (100 mg/m^2)	II	NCT04369937$^{(R)}$
	Paclitaxel/Cisplatin *vs.* Docetaxel/Cisplatin	Paclitaxel (260 mg/m^2), Cisplatin (75 mg/m^2) *vs.* Docetaxel (75 mg/m^2), Cisplatin (75 mg/m^2)	IV	NCT04766827$^{(R)}$
Prostate Cancer	Pembrolizumab/Etoposide/ /Cisplatin	no data	I	NCT03582475$^{(R)}$
Testicular Cancer	Bleomycin/Etoposide/Cisplatin *vs.* Carboplatin	no data	III	NCT02341989$^{(ANR)}$
	Etoposide/Cisplatin/Radiation Therapy	Etoposide (100 mg/m^2), Cisplatin (20 mg/m^2), Radiotherapy (2 Gy — 3 weeks later)	II	NCT03937843$^{(R)}$

$^{(ANR)}$ — active, not recruting; $^{(NR)}$ — not yet recruiting; $^{(R)}$ — recruiting

peutic treatment regimen for NSCLC includes, *inter alia*, administration of cisplatin in combination with paclitaxel. The effective interaction of cisplatin with nab-paclitaxel in relation to advanced NSCLC cancer was reported by Hattori et al [74] in Phase I and II clinical trials. Hayashi et al. [75] suggested the possibility of concurrent use of cisplatin in combination with nab-paclitaxel and radiation therapy for the treatment of locally advanced NSCLC. When assessing the effectiveness of the therapy in Phase I/II clinical trials, it was shown that concurrent chemoradiotherapy in combination with cisplatin and nab-paclitaxel can be a promising method of treatment for NSCLC in patients under 75 years of age, with normal renal function [75]. There are still ongoing studies evaluating the effectiveness of cisplatin and paclitaxel with, among others, sintilimab (Identifier: NCT04840290), pemetrexed and tislelizumab (Identifier: NCT04379635) [73]. An alternative in the treatment of lung cancer is also the combined action of cisplatin with vinorelbine [76]. In contrast, in an experimental animal model, it has been shown that cisplatin in combination with erlotinib can be effective in inhibiting tumor growth in lung cancer [77]. Phase I clinical trials (Identifier: NCT04809103) are currently underway to determine the maximum dose of tolerated cisplatin administered bronchoscopically to the tumor in patients diagnosed with NSCLC [73].

Breast cancer

In the second phase of clinical trials, Rosati et al. [78] observed that in patients with metastatic breast cancer resistant to anthracyclines, a well-tolerated chemotherapy regimen may be a treatment based on the combination of cisplatin and paclitaxel. However, it has been shown that an adverse reaction resulting from the use of this therapy was increased neurotoxicity [78]. According to the literature data, the combined effect of cisplatin and gemcitabine may also be very effective in the treatment of breast cancer [79]. It was found that the combination of cisplatin with gemcitabine, despite the observed side effects [80], may have a beneficial therapeutic effect and constitute an alternative treatment for patients with triple-negative metastatic breast cancer (TNBC) [79, 80]. Similar conclusions were presented after the combined action of cisplatin with nab-paclitaxel [81]. High therapeutic activity and a mild toxic profile were obtained in Phase II clinical trials (Identifier: NCT01928680) as a result of TNBC treatment with cisplatin and capecitabine, initiated after initial treatment with anthracyclines and taxanes [73, 82].

Ovarian cancer

The use of cisplatin in the treatment of ovarian cancer has proved to be an important chemotherapy strategy. In the treatment of advanced ovarian cancer, the treatment regimen based on the use of cisplatin with paclitaxel [83] and cisplatin with cyclophosphamide [84] was also assessed. Phase III studies conducted by Mouratidou et al. [84] suggest a stronger response of ovarian cancer cells to cisplatin with paclitaxel therapy than to cisplatin with cyclophosphamide although with no clear differences in disease progression and survival time. In palliative chemotherapy, in the treatment of advanced or recurrent ovarian cancer, it has been observed that the combination of cisplatin and topotecan may be highly effective. However, this activity was associated with the unfavorable effect of the complexes on hematological indicators [85]. Hoskins et al. [86], in the assessment of Phase III clinical trials, did not observe significant changes in the pharmacological efficacy of the combined effect of cisplatin with topotecan in relation to carboplatin and paclitaxel therapy. Reports from literature data indicate that the use of cisplatin with doxorubicin may be beneficial in the treatment of ovarian cancer [87]. Moreover, in women with advanced and inoperable ovarian cancer, high efficacy was observed after combining cisplatin with doxorubicin in intraperitoneal negative pressure aerosol chemotherapy [87]. Phase II studies have also been implemented to evaluate the dosing regimen and pharmacodynamics of cisplatin used as intraperitoneal chemoperfusion in women with stage III epithelial ovarian cancer (Identifier: NCT02567253) [73].

Bladder cancer

First-line chemotherapy based on cisplatin is one of the basic treatments for advanced urothelial tumors [88]. In metastatic bladder cancer, standard cancer therapy includes methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC regimen) [89]. Literature data indicate that cisplatin and gemcitabine chemotherapy may also have a beneficial effect in the treatment of advanced bladder cancer [88]. This therapy is also used in neoadjuvant treatment [89]. The use of cisplatin with gemcitabine in induction chemotherapy has also been suggested in patients with invasive bladder cancer [90, 91] although the obtained results of Phase III clinical trials were inconclusive and called for further analyzes [90]. Okabe et al. [89] observed that cisplatin and gemcitabine cumulative treatment of infiltrating bladder cancer shows a therapeutic effect comparable to the MVAC regimen. In addition, treatment based on the combined effect of cisplatin with atezolizumab and pembrolizumab may gain recognition in the treatment of advanced and metastatic urothelial neoplasms [73].

Head and neck cancer

The standard topical treatment for advanced squamous cell neoplasms of the head and neck is cisplatin chemotherapy with radiotherapy [92]. Studies determin-

ing the dosing regimen of cisplatin used concurrently with radiotherapy are still ongoing [93, 94]. The efficacy of cisplatin in induction chemotherapy in advanced, inoperable head and neck cancer has also been observed in combination with 5-fluorouracil [95], as well as in a regimen with fluorouracil and docetaxel [92]. Yokota et al. [92] showed that in the treatment of head tumors, chemoradiotherapy initiated after previous induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (cisplatin was given in divided doses) may have a beneficial therapeutic effect and low toxicity. Moreover, Fietkau et al. [96], comparing chemoradiotherapy regimens in advanced head and neck cancer in Phase III clinical trials, found that a reduced dose of radiotherapy with concomitant cisplatin and paclitaxel has a therapeutic effect comparable to standard chemoradiotherapy, with cisplatin and fluorouracil.

Prostate and testicular cancer

Literature data indicate that first-line treatment of prostate cancer includes docetaxel therapy [97]. In Phase II clinical trials, it has been observed that, after prior docetaxel treatment, a beneficial therapeutic effect can be obtained after administration of cisplatin with prednisone [98]. Chemotherapy based on the combined action of cisplatin with gemcitabine may also be effective in the treatment of advanced prostate cancer [99]. Cisplatin-based therapy is also the standard treatment for testicular cancer. The use of cisplatin in the treatment of testicular cancer has contributed to the improvement of the therapeutic efficacy and an increase in the cure rate since the 1980s [100]. Currently, the standard treatment of testicular cancer includes the BEP regimen using cisplatin, etoposide, and bleomycin [101]. Phase III clinical trials are also conducted to compare the effectiveness of the multi-drug BEP regimen and the dose-dense combination chemotherapy containing cisplatin, etoposide, bleomycin, paclitaxel, oxaliplatin, and ifosfamide in patients with stage II or stage III non-seminomatous germ cell (Identifier: NCT00104676) [73].

Summary

The high efficacy of cisplatin in the treatment of malignant neoplasms may be limited by developing cellular resistance and numerous side effects. Currently, research is being conducted to find and implement new therapeutic strategies using cisplatin, also in combination with other chemotherapeutic agents and substances with potential anti-cancer properties. Perhaps the use of cisplatin in new multi-drug therapy regimens will contribute to increasing the effectiveness of oncological treatment.

Conflict of interest

Authors declare no conflict of interest.

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