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Selected platinum complexes in standard and modern anti-cancer therapies

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The constantly observed increase in the number of cancer cases inspires research aimed at searching for new compounds with anti-cancer potential. In recent years, much research has focused on platinum complexes, especially their anti-cancer properties. Platinum derivatives are characterized by high cytotoxic activity against many types of cancer cells. However, among the numerous developed complexes, only cisplatin, carboplatin and oxaliplatin have found wide application in chemotherapeutic treatment. Nedaplatin, lobaplatin and heptaplatin have also gained recognition, and have been implemented in oncological therapy in Japan, China and Korea. Some of the platinum complexes are still at the stage of pre-clinical and clinical trials. The aim of the research conducted today is to search for platinum compounds that show high pharmacological effectiveness, with clearly limited side effects. In future therapeutic strategies, the possibility of using platinum complexes in conjunction with other chemotherapeutic compounds is being considered, which may contribute to increasing the efficacy of anti-cancer therapy.

Key words: cisplatin, platinum complexes, anticancer drugs, chemotherapy

Introduction

According to the National Cancer Registry, cancer diseases, along with cardiovascular diseases, are the most common cause of death in Poland [1, 2]. Literature data show that the number of patients with neoplastic diseases may systematically increase, and cancer may become the main cause of premature deaths, for both women and men [3]. The most frequent cases of cancer are lung, ovarian, cervical, prostate, testicular, stomach and colon cancers. In addition to many currently used methods of treating oncological diseases, it is important to implement appropriate preventive measures in everyday life, which would significantly slow down the processes of carcinogenesis.

The etiology of neoplastic diseases is complex and multifaceted, conditioned by both external (environmental) and internal factors [4]. It has been shown that some behavioral and psychosocial factors (including stress and depression) as well as genetic predispositions may contribute to the development and progression of neoplastic diseases [5–7]. An improper diet, low physical activity and chronic stress are more and more often mentioned as some of the basic indicators influencing the development of the carcinogenesis process [5–7, 8, 9].

Despite the wide range of preventive tests implemented, the development of diagnostic techniques and the constantly growing public awareness, it has still not been possible to find appropriate therapeutic methods that would effectively combat all types of cancer. In recent years, special attention has been paid to the side effects of treatment, resulting from the high toxicity of the cytostatics used [10, 11]. It was also

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noticed that the problem of cancer cells resistance to the drugs used is becoming more and more frequent [12, 13]. Numerous metal compounds, including platinum and its derivatives, play an important role in the treatment of neoplastic diseases. Currently, some platinum complexes are used effectively in the chemotherapy of malignant neoplasms. However, there are still some platinum derivatives whose anti-tumor activity is not yet sufficiently known and described.

The aim of this study is to explain the most important mechanisms of action of the selected platinum compounds, their potential therapeutic properties, and to determine the role of new platinum complexes that would be characterized by low toxicity over a broad spectrum of anti-tumor activity.

Platinum complexes in anti-cancer therapy

Due to the multidirectional scope of action of platinum, platinum drugs are now quite widely used in the treatment of cancer. One of them is the platinum compound (II) called cisplatin. It was introduced to clinical practice at the earliest, in the literature it is described as a first-generation platinum drug. The confirmation of the anti-cancer effect of cisplatin has resulted in the search for other platinum complexes, effective in anti-cancer therapy, but with limited side effects [14]. In recent years, a number of *in vitro* and *in vivo* studies have been conducted to determine the potential anti-tumor properties of cisplatin analogues. Of these, only carboplatin and oxaliplatin are used in oncological therapy, and a number of others (picoplatin, phenanthriplatin, satraplatin, adamplatin, oxoplatin, ethacraplatin, lipoplatin, BBR3464) are still at the experimental or clinical trial stage (tab. I). The mechanisms underlying the anti-tumor activity of the new platinum (II) and (IV) complexes are still insufficiently elucidated. It is known, however, that platinum compounds are characterized by quite diverse therapeutic effects, which may result from a different chemical structure, geometric isomerism and the degree of oxidation of platinum [15].

Cisplatin – a first-generation platinum drug

Cisplatin was first synthesized by Alfred Werner in 1845, and its chemical structure was described in 1893. In 1965, Barnett Rosenberg showed that platinum complexes generated during electrolysis significantly weaken the multiplication of *Escherichia coli* bacteria [14, 16]. This discovery became the basis for further research aimed at determining the inhibitory effect of cisplatin on the proliferation of cancer cells. It was then revealed that the compound can effectively inhibit cell division of murine sarcoma and L1210 leukemia [16]. In clinical practice, cisplatin was first used in 1971, while 7 years later this compound was approved by the Food and Drug Administration (FDA) and became an available drug with an anti-cancer effect [17–19]. Currently, cisplatin is used with great effectiveness in the treatment of breast, ovarian, cervical, prostate, testicular, esophagus, stomach, head and neck cancer, multiple myeloma, melanoma, non-Hodgkin's lymphoma and cell lung cancer [17, 18, 20].

The drug can be used both as monotherapy and in combination therapy with radiotherapy, taxoids (paclitaxel and docetaxel), doxorubicin, 5-fluorouracil, leucovorin and gemcitabine. The combined effects of cisplatin and other compounds in the treatment of various types of cancer are still undergoing numerous experimental and clinical evaluations [21–23]. Cisplatin has been shown to be highly effective in the treatment of neoplastic diseases, but at the same time it has been found to be highly toxic to normal cells. Side effects are multi-organ, include cardiotoxicity, ototoxicity, myelosuppressive and immunosuppressive activity [17, 24–26]. Moreover, cisplatin is a highly nephrotoxic drug leading to the development of acute renal failure, which may significantly impede dosing of the drug and limit its use [17, 27, 28].

Cisplatin is a cytostatic, belonging to the group of drugs with an alkylating effect [13]. It has pro-apoptotic [20, 29–31] and antiproliferative [20, 32, 33] properties, which allows it to be used in the treatment of many types of malignant neoplasms. However, it is important to remember about the factors influencing the effectiveness of cisplatin treatment, such as: the diverse biological response of cancer cells, various sensitivity and resistance to the drug. Neoplastic cell resistance to cisplatin may lead to disease recurrences, sometimes shortly after chemotherapy has been completed.

The mechanisms underlying platinum resistance are complex and are currently not fully understood. This process is multifactorial in nature. In general, several signals are activated simultaneously, which weaken the effectiveness of the therapy [33]. This is a key problem in overcoming the resistance of cancer cells to cisplatin. Therefore, it is extremely important to conduct research that will allow an explanation of the interaction between the factors, responsible for both the sensitivity and resistance, of cancer cells to the action of platinum complexes.

Cisplatin analogues currently used in cancer chemotherapy

The available literature shows that cisplatin is a long-used anticancer drug showing high toxicity and numerous dose-dependent side effects [17, 32–36]. In addition, acquired resistance to this drug has been found [33–35]. These data inspired the search for new compounds with cisplatin-like properties but with high therapeutic efficacy and limited adverse effects on normal cells. The platinum derivatives, carboplatin and oxaliplatin, turned out to be drugs with a broad spectrum of antitumor activity, with low toxicity and reduced acquired resistance. In addition to carboplatin and oxaliplatin, which have been approved and introduced in medicine, the platinum complexes such as nedaplatin, lobaplatin and heptaplatin are also gaining recognition. To date, only a few Asian countries have obtained consent to use these compounds in oncological therapy (tab. I).

Table I. Selected platinum complexes in contemporary and future therapeutic strategies [18, 36, 37, 71, 77, 96]. Current status as of July 2021

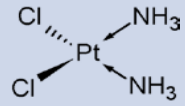
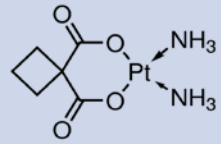
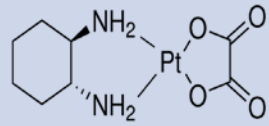
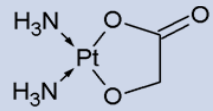
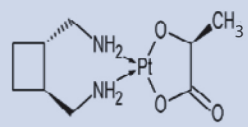
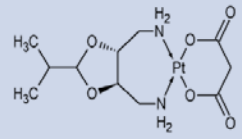
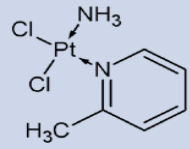
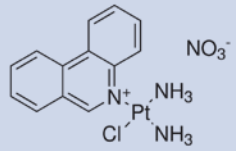
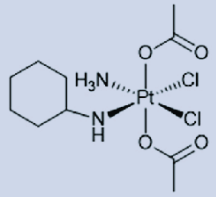
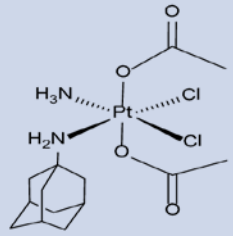
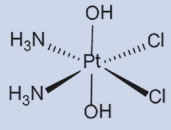
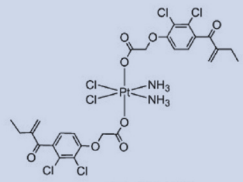
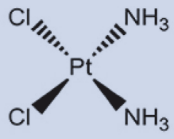
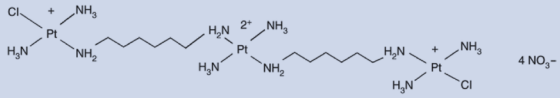
Platinum complex		Molecular formula	Structure	Clinical or experimental status
PLATINUM COMPLEXES (II)	cisplatin platinol	cis-dichlorodiammine platinum $Pt(NH_3)_2Cl_2$		The drug was approved by the FDA. It has been used in medicine since 1978.
	carboplatin paraplatin	cis-diammine(1.1-cyclobutanedicarboxylato) platinum $[C_4H_6(CO_2)_2]Pt(NH_3)_2$		The drug was approved by the FDA. It has been used in medicine since 1989.
	oxaliplatin eloxatin	(trans-R,R-cyclohexane-1.2-diammine) oxalatoplatinum [SP-4-2-(1R-trans)]-(1.2-cyclohexanediamine-N,N')[ethanedioata(2--)-O,O']platinum (DACH)$PtCl_2$ $C_8H_{14}N_2O_4Pt$		The drug was approved by the FDA. It has been used in Europe since 1999 and in the USA since 2002.
	nedaplatin aqupla	cis-diammine(glycolato)platinum $C_2H_8N_2O_3Pt$		The drug has been used in Japan since 1995. It is still the subject of numerous clinical trials.
	lobaplatin D-19466	1,2-diammino-1-methyl-cyclobutane-platinum-lactate $C_9H_{18}N_2O_3Pt$		The drug has been used in China since 2004. It is still the subject of numerous clinical trials..
	heptaplatin SKI-2053R sunpla	cis-malonato[(4R,5R)-4.5-bis(aminomethyl)-2-isopropyl-1.3-dioxolane]platinum $C_{11}H_{22}N_2O_6Pt$		The drug has been used in Korea since 2005..
	picoplatin AMD473 JM473 ZD0473	cis-diammine-dichloro (2-methylpyridine)platinum $C_6H_{10}Cl_2N_2Pt$		The compound is in clinical trials.
	phenanthriplatin	(SP-4-3)-diamminechlorido(phenanthridine) platinum nitrate, cis-Pt(NH3)2(phenanthridine)Cl]NO_3 cis-[Pt(NH3)2Cl(phenanthridine)]$^+$ $C_{13}H_{15}ClN_4O_3Pt$		The compound is at the stage of experimental research..
PLATINUM COMPLEXES (IV)	satraplatin JM216	bis-acetato-amminedichloro (cyclohexylamine) platinum $C_{10}H_{22}Cl_2N_2O_4Pt$		The compound is in clinical trials.
	adamplatin LA-12	trans-[$PtCl_2(CH_3COO)_2(NH_3)$ (1-adamantylamine)] $C_{14}H_{26}Cl_2N_2O_4Pt$		The compound is at the stage of experimental research.
	oxoplatin	cis-diammine-dichlorido-trans-dihydroxy-platinum $Cl_2H_8N_2O_2Pt$ $Pt(NH_3)_2Cl_2(OH)_2$		The compound is at the stage of experimental research.

Table I. cont. Selected platinum complexes in contemporary and future therapeutic strategies [18, 36, 37, 71, 77, 96]. Current status as of July 2021

Platinum complex		Molecular formuła	Structure	Clinical or experimental status
	ethacraplatin	cis,cis,trans-diamminodichloridobis (ethacrynato)platinum		The compound is at the stage of experimental research.
PLATINUM COMPLEX PACKED IN LIPOSOMES	lipoplatin liposomal cisplatin	encapsulated cis-diammine-dichloroplatinum(II)		The compound is in clinical trials.
TRI-NUCLEAR PLATINUM COMPLEX	BBR3464 triplatin tetranitrate	((trans-PtCl(NH$_3$)$_2$)$_2$-(trans-Pt(NH$_3$)$_2$ (NH$_2$(CH$_2$)$_6$NH$_2$)$_2$)NO$_3$)$_4$ $C_{12}H_{50}Cl_2N_{14}O_{12}Pt_3$		The compound is in clinical trials.

Carboplatin

Carboplatin is a second generation platinum compound with a structure similar to cisplatin. In the structure of carboplatin, instead of chlorine atoms, there is a 1.1-cyclobutyl dicarboxylic anion [36–38]. After penetrating the cell membrane, this compound is hydrolyzed to active forms, this process is much slower than the hydrolysis of cisplatin, therefore carboplatin may be better tolerated by patients. Through covalent bonds with N7 purine atoms, it forms adducts with DNA analogous to cisplatin, so that the mechanism of its biological activity is similar to that of cisplatin [25, 39]. The binding of carboplatin to the DNA of neoplastic cells leads to changes in the nucleic acid structure and inhibition of the replication process. This results in the induction of apoptosis and determines the cytotoxic properties of the compound [40]. The kinetics of carboplatin binding to DNA, however, is much slower than that of cisplatin. The slow hydrolysis of carboplatin shows, depending on the type of cancer, reduced effectiveness of the therapeutic effect compared to the effect of cisplatin [18, 41]. Literature data show that in order to obtain a cytotoxic effect similar to cisplatin, it is necessary to use up to 10 times higher doses of carboplatin [42]. Currently, carboplatin is used in the treatment of ovarian cancer of epithelial origin and non-small-cell lung cancer, and it is also administered in multi-drug therapy in the case of insufficient tolerance of the organism to cisplatin treatment [43]. The use of carboplatin in combination with taxoids and vincristine has also been suggested in the treatment of malignant tumors of the testicle, head and neck, cervical and breast cancer, and malignant glioma [39, 44–46]. Despite the lower pharmacological efficacy of carboplatin, a positive aspect of its use is its reduced systemic toxicity, especially its nephrotoxicity. On the other hand, an adverse effect demonstrated with carboplatin therapy is bone marrow dysfunction [47].

Oxaliplatin

Oxaliplatin is a platinum drug of the 3rd generation, the structure of which incorporates, in place of the amine ligands, a 1.2-diaminocyclohexane (DACH) group, which determines the cytotoxic activity of this complex [48]. This drug inhibits DNA repair processes, leading to inhibition of the cell cycle and increasing the sensitivity of cancer cells to signals from the apoptotic pathway [49]. Oxaliplatin exhibits a biological effect similar to first and second generation platinum drugs, consisting in the formation of specific adducts with DNA, interfering with replication and transcription of the deoxyribonucleic acid double helix [50]. As a result of oxaliplatin biotransformation, a secondary metabolite other than for cisplatin and carboplatin (trans-diaminacyclohexane-dihydroxy-platinum [II]) is formed, which may result in a different pharmacokinetic profile of the drug and various toxic effects [43, 48]. Oxaliplatin has been shown to have a relatively low activity in monotherapy, so it is most often administered in combination with other chemotherapeutic compounds (e.g., fluorouracil, irinotecan, leucovorin, ifosfamide, etoposide and gemcitabine) [48, 51]. Currently, this drug is used mainly in the multi-drug therapy of testicular, stomach and pancreatic cancer, breast cancer, non-Hodgkin's lymphoma and neoplasms showing resistance to cisplatin and carboplatin [37]. High efficacy in the treatment of advanced and platinum-resistant cancers of the colon has been demonstrated after combining oxaliplatin with 5-fluorouracil and leucovorin [52]. Currently, oxaliplatin is successfully used in the treatment of gastric cancer, however, clinical trials are still being conducted to evaluate the effectiveness of oxaliplatin therapy in combination, among others with S-1 (a prodrug of 5-fluorouracil) [53, 54]. Oxaliplatin, like other platinum drugs, can also cause side effects. Chelation of extracellular Ca^{2+} ion may disrupt the function of sodium channels and induce acute or chronic peripheral neuropathy [42, 51].

Nedaplatin

Nedaplatin is a cisplatin analogue, a second-generation drug developed in 1983 in Japan. Like cisplatin and carboplatin, its chemical structure has two amine ligands and additionally a glycolic acid dianion [55]. Nedaplatin undergoes hydrolysis, which leads to the formation of a pharmacologically active secondary metabolite (cis-diaminadihydroxyplatin [II]), analogous to cisplatin and carboplatin, capable of forming coordination bonds with DNA bases [43]. This compound is characterized by a reduced nephrotoxic effect and therapeutic effectiveness similar to carboplatin [55]. Nedaplatin has a beneficial effect on squamous cells in lung cancer, head and neck cancers. This drug can be used in patients with recurrent changes of cervical and ovarian cancer after treatment with cisplatin [56]. Nedaplatin can also be used in patients with hypersensitivity reactions to carboplatin therapy [57]. In clinical trials, nedaplatin has been shown to be highly effective pharmacologically in combination with radiotherapy, paclitaxel and irinotecan [58–60]. In combination therapy, its high effectiveness has also been found in the treatment of malignant urological tumors [61].

Lobaplatin

In turn, lobaplatin is a third generation platinum drug. In China, this drug has been approved for the treatment of advanced breast cancer, small-cell lung cancer and chronic myeloid leukemia [62, 63]. According to the literature, lobaplatin is also effective in the treatment of malignant neoplasms of the ovary, cervix, large intestine and stomach [64, 65]. It has been observed that in the treatment of gastric cancer, the antitumor effect of lobaplatin may enhance its combined effect with paclitaxel [62]. It is possible that paclitaxel enhances the effect of lobaplatin and reduces drug resistance by inhibiting the PI3K/Akt pathway also in lung cancer cells [66]. Increased sensitivity of cancer cells to radiation and to the pro-apoptotic activity of lobaplatin was revealed in its cumulative action with radiotherapy [67]. The preliminary results of *in vitro* and *in vivo* studies show that lobaplatin may have antitumor efficacy higher than carboplatin, with limited nephro-, neuro- and ototoxicity [68]. Nevertheless, a side effect limiting the use of the drug is the found thrombocytopenia [69].

Heptaplatin

Heptaplatin is a 3rd generation platinum complex with a slight undesirable nephrotoxic effect. It was assumed that the mechanism of its therapeutic action was similar to that of cisplatin and oxaliplatin [70]. In Korea, this drug has been approved for the treatment of advanced stomach tumors [71]. A wide spectrum of anti-tumor activity of heptaplatin was observed in phase I and II clinical trials against gastric, head and neck cancer cells, also in combination therapy with 5-fluorouracil and leucovorin [72–74]. Heptaplatin has also been shown to be effective in the treatment of L1210 cisplatin-resistant leukemia cells [72]. Presumably, the activity of the drug may be partly related to the decreased expression of metallothioneins as a result of heptaplatin action [72].

However, the exact mechanisms of the biological actions of heptaplatin have not yet been fully elucidated.

Therapeutic strategies for new platinum complexes

Since the treatment of neoplastic diseases with classic platinum drugs, apart from their high efficiency, is burdened with many side effects, the search for new platinum complexes, analogous to cisplatin but with low toxicity, is still being sought. Promising platinum compounds at the stage of clinical trials include, among others: picoplatin and phenanthriplatin.

Picoplatin

A new generation of platinum (II) compounds with significant anti-cancer potential is picoplatin. The mechanism of action of picoplatin is similar to that of cisplatin. It consists in creating specific bonds with DNA, although the resulting adducts show greater selectivity of action [37]. The 2-methylpyridine group present in the chemical structure of the compound slows down its intracellular hydrolysis and binding to DNA, which may possibly affect the profile of pharmacological activity and reduced toxicity of the complex [75]. Picoplatin has been shown to be highly effective in treating ovarian and lung cancer that are resistant to cisplatin and carboplatin treatment [76]. This compound was subjected to phase II and III clinical trials, in which the antitumor activity of picoplatin in the treatment of small-cell lung cancer was assessed. In contrast, phase I clinical trials focused on the efficacy of picoplatin in monotherapy in non-haematological malignancies and in combination with 5-fluorouracil and leucovorin in the treatment of colorectal cancer. Phase I studies also focused on the combination of picoplatin and docetaxel in the treatment of hormone refractory prostate cancer and the cumulative effect with liposomal doxorubicin in the treatment of lymphoma and small intestine cancer [77].

Phenanthriplatin

A monofunctional platinum (II) complex, implemented to overcome the mechanisms of cancer cell resistance, is phenanthriplatin, which contains a phenanthridine ligand in its structure. This complex, by means of covalent bonds, with high efficiency, forms adducts with DNA, a result of which means it strongly inhibits the transcription process [19]. Presumably, the DNA-binding profile of phenanthriplatin is different from that of cisplatin, which influences its different biological activity [78]. Although the mechanism of action of phenanthriplatin has not been fully established, it has been observed that this compound may act on cancer cells with greater efficiency than cisplatin and oxaliplatin [79]. The interaction of the complex with organic cation transporters (OCT) contributes to the strong effect of phenanthriplatin on tumor cells, which may

suggest that OCT overexpressing tumor cells (e.g. colon cancer) are particularly sensitive to the therapeutic effect of this compound [80]. Moreover, the increased cytotoxic activity of the complex may result from increased cellular uptake [79]. Phenanthriplatin-induced cell death may also result from impaired ribosome biogenesis and increased activation of the L11 ribosomal protein, which, by inhibiting Mdm2 binding to p53, triggers an apoptotic signal [81]. Phenanthriplatin inhibits the mechanisms related to the development of cellular resistance, therefore it may be effective in cancer cells resistant to cisplatin therapy [79, 80]. The beneficial effect of phenanthriplatin has been demonstrated, among others, by on small-cell lung cancer lines [78, 82, 83]. However, in preliminary analyses of clinical trials, significant adverse effects caused by phenanthriplatin were observed, therefore the assessment of its cytotoxic properties is still based on ongoing experimental studies.

Platinum (IV) complexes in anti-cancer therapy

In order to change the biological and chemical properties and improve the pharmacokinetic effects of platinum drugs, the degree of platinum oxidation was modified. In addition to platinum (II) compounds, platinum (IV) compounds have been synthesized. The literature data show that changing the geometry of the molecule from polar to octahedral results in the production of compounds with specific pharmacological properties [15]. Platinum (IV) derivatives are defined as prodrugs which, when reduced to Pt (II) forms, are only activated inside the cell [84]. Platinum (IV) compounds are characterized by increased kinetic activity, lipophilicity and stability, relatively low toxicity and increased activity against drug-resistant cells [85]. The advantage of platinum (IV) complexes is the possibility of their oral use, which can significantly facilitate the form of therapy and improve the quality of life of patients [85].

Satraplatin

Satraplatin is an example of a platinum (IV) complex. It is an analog of carboplatin containing two acetyl groups in its chemical structure, this largely contributes to the increased lipophilicity of the compound and its bioavailability [43]. Increased intracellular biotransformation of satraplatin leads to the formation of the active metabolite (JM118, $PtCl_2$ [NH_3] [cha]) [37, 61]. The spectrum of anti-cancer activity of this drug includes platinum-resistant cancer cells of the cervix, prostate, ovary and lungs [61]. The clinical trials performed included the I, II and III phase of the assessment of the antitumor effect in the treatment of prostate cancer, both as monotherapy and in combination with prednisone. In turn, the effect of co-administration of satraplatin with erlotinib and paclitaxel was assessed in relation to breast and lung cancer. Phase I studies also assessed the efficacy of satraplatin in combination with docetaxel and paclitaxel in the treatment of advanced solid tumors. Detailed studies are currently underway to determine the effect of satraplatin in the treatment of patients with high-risk prostate cancer [77].

Adamplatin

An analog of satraplatin with an equally high lipophilicity is adamplatin (IV). This compound is characterized by a broad spectrum of activity, through increased accumulation inside cells, strong inhibition of DNA polymerization and impaired repair of DNA structure damage [15]. Increased cellular uptake of the complex also influences the anti-cancer effect of adamplatin [86]. In addition, sulfur-containing compounds may play a less important role in the mechanisms of cell resistance to adamplatin than to cisplatin. Significant cytotoxic activity of adamplatin was found in in vitro studies against colon cancer cells, leukemia and ovaries, as well as cell lines resistant to cisplatin therapy [84]. Currently, adamplatin has not been implemented in clinical trials.

Oxoplatin

Another platinum (IV) compound with potential anti-cancer properties is oxoplatin. This complex was first synthesized in 1927 by Chugaev and Khlopin [85]. Oxoplatin is activated inside the cell in the presence of ascorbic acid and hydrogen chloride, therefore, oral administration of the compound can significantly accelerate and enhance its biological activity [87]. The increased distribution of this complex in the blood helps to quickly reach the target site of action. The *in vitro* studies conducted so far show that oxoplatin has a prolonged therapeutic effect and higher pharmacokinetic activity than cisplatin. It has also been found that it inhibits the growth of neoplastic tumors more than cisplatin and may weaken the process of distant metastases [85]. The cytotoxic properties of oxoplatin have been observed in vitro in neoplastic cells of the pancreas, colon, prostate and stomach [85, 88]. However, the mechanism of action of this compound has, as yet, not been fully determined.

Ethacraplatin

So far, the spectrum of the biological and pharmacotherapeutic effects of ethacraplatin (IV) on cancer cells is unexplained. Ethacraplatin is a cisplatin molecule linked to two ethacrynic acid ligands and has the ability to inhibit the activity of glutathione transferase (GST) [89]. This mechanism of action accelerates the formation of adducts with DNA, promotes damage, reduces cellular resistance and thus enhances the pro-apoptotic properties of the complex. However, ethacraplatin is characterized by antitumor activity with a relatively short duration of action [90]. Therefore, work is currently underway to develop encapsulated ethacraplatin, which will increase the amount of the preparation directly in neoplastic tissues, which may contribute to the improvement of therapeutic efficacy in platinum-resistant cells [89].

Liposomal platinum complexes

In order to reduce the nephrotoxicity of platinum complexes and increase their antitumor activity, drug carriers have been

designed, e.g. liposomes. To date, two liposomal CDDP compounds have been developed: SPI-077 and lipoplatin [61, 91].

The SPI-077 preparation was characterized by an extended half-life and a fairly good tolerance of the organism, but it showed a relatively low therapeutic activity observed in phase I and II clinical trials. The insufficient therapeutic effect of SPI--077 was most likely due to the limited release of cisplatin from liposomes inside the tumors [92].

Lipoplatin

Clinical trials are currently underway to assess the therapeutic properties of lipoplatin. Lipoplatin nanoparticles with a diameter of 110 nm, covered with a polymer coating, consist of a lipid envelope and a central core composed of a cisplatin molecule. The lipid layer consists of: cholesterol, phosphatidylcholine, soybeans, dipalmitoylphosphatidylglycerol and methoxypolyethyleneglycol conjugated with disteroylphosphatidylethanolamine [91, 93, 94]. The lipid layer of nanoparticles facilitates their transport to cancer cells by endocytosis [95]. The mechanism of action of lipoplatin is based on the increased accumulation of cisplatin molecules in the tissues of primary tumors and metastatic sites. On the other hand, the accumulation of the drug in neighbouring healthy cells was many times lower [92, 95]. This is because the drug can penetrate the blood vessel endothelium directly within the neoplastic lesions [93]. By releasing the cisplatin molecule, lipoplatin activates the mitochondrial apoptotic pathway [95]. The liposomal form of cisplatin reduces systemic toxicity and enhances the anti-cancer effect by targeting the drug directly into the tumor [94]. To date, phase I and II clinical trials have been conducted to assess the anti-tumor effect of liposomal cisplatin as monotherapy in the treatment of osteosarcoma and phase III of the treatment of pancreatic cancer in combination with fluorouracil and gemcitabine. The phase I clinical trials also concerned the efficacy of lipoplatin in patients with pleural malignancies after verteporfin therapy. The research evaluating the effects of liposomal cisplatin in the treatment of advanced and refractory solid tumors (phase I) and breast, prostate and skin cancer (phase II) are still ongoing [77].

Multi-core platinum complexes

New therapeutic possibilities are also created by platinum multi-core complexes, which have been developed to increase the platinum-to-DNA binding capacity. Among them, one can distinguish two- and three-core complexes containing at least two platinum atoms in their structure [96]. The BBR3464 gained the greatest recognition among multi-core complexes.

BBR3464

In the chemical structure of the compound, based on the structure of cisplatin, there are two monofunctional groups [trans-$PtCl(NH_3)_2$]platinum, linked by platinum tetra-amine (trans-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2)^{2+}$ [97]. The unique structure of BBR3464 ensures increased cellular uptake and enhanced DNA binding resulting from the appropriate electrostatic interaction and the formation of hydrogen bonds [97, 98]. BBR3464 adducts formed from DNA differ significantly from those created as a result of fusion with cisplatin, which may provide a higher therapeutic activity of the complex [98]. This compound is characterized by a prolonged pharmacological effect, which results in the inhibition of the growth of neoplastic tumors even after the end of therapy. This may indicate that the mechanism of action of BBR3464 on cell cycle disorders is different from that of cisplatin [97, 99]. *In vitro* and *in vivo* studies have demonstrated the high efficacy of BBR3464 in cisplatin sensitive and resistant tumors, as well as in cells with a mutation of the p53 oncosuppressive gene [99]. Proapoptotic properties of BBR3464 have been observed against ovarian cancer cells and malignant melanoma [97, 100]. In preclinical studies, the cytotoxic activity of BBR3464 was noted at concentrations several times lower than in cisplatin [75]. However, in a clinical evaluation, the antitumor activity of the complex was diversified, depending on the type of neoplastic cells. BBR3464's inadequate efficacy in some cancers, including gastric cancer may result from the increased metabolic degradation of the compound, which leads to the development of a more appropriate pharmacokinetic profile [97]. To date, BBR3464 has undergone phase II clinical trials to determine its cytotoxic effect against adenocarcinoma of the pancreas and small-cell lung cancer [77].

Conclusions

The discovery and approval of cisplatin for the treatment of cancer at the turn of the 20th century was of great importance for modern oncological medicine. Currently, cisplatin is one of the basic cytostatics used in the treatment of neoplastic diseases, both as monotherapy and in multi-drug therapy in combination with other anticancer compounds. Understanding the broad spectrum of anti-cancer activity of cisplatin has contributed to the search for new platinum complexes showing high therapeutic efficacy, with limited side effects, and the possibility of overcoming platinum resistance. The unique properties of the new platinum complexes may contribute to their wider use in anti-cancer therapy in the future.

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