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Comparative Analysis of Clinical Trials, Therapeutic Uses, Pharmacokinetics, and Adverse Effects of Approved Platinum-Based Drugs

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ABSTRACT

Platinum-based complexes represent some of the most widely used anticancer agents. This study aims to collect, analyze, and comparatively evaluate clinical trials and therapeutic indications of currently approved platinum derivatives, including Cisplatin, Carboplatin, Oxaliplatin, Nedaplatin (Japan), Lobaplatin (China), Heptaplatin (North Korea), and Satraplatin. Another objective is to summarize the historical development of these drugs and to compare their pharmacokinetic properties, adverse effects, and dose-limiting factors. Observational data on pharmacokinetics indicate that protein binding decreases in the following order: Cisplatin (95%), Oxaliplatin (90%), Nedaplatin (50%), and Carboplatin (low). More than 1000 clinical trials have been reported for each of Cisplatin, Carboplatin, and Oxaliplatin, whereas Lobaplatin, Nedaplatin, and Satraplatin have approximately 10 trials each. Differences in dose-limiting toxicities include neurotoxicity, nephrotoxicity, and ototoxicity for Cisplatin; neurotoxicity for Oxaliplatin; nephrotoxicity for Heptaplatin; and myelosuppression—manifesting as thrombocytopenia, neutropenia, or leukopenia—for Carboplatin, Nedaplatin, and Satraplatin.

Keywords: Limiting factors, Application, Cisplatin derivatives, Pharmacokinetics

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Introduction

Malignant tumors are the leading cause of death worldwide and comprise over 100 distinct disease types characterized by uncontrolled cellular proliferation, local tissue invasion, and distant metastasis. The incidence of these tumors is rising, with lung, prostate, and colon cancers showing the fastest growth in men, and breast cancer being the most prevalent in women. Tumors can arise from various tissues, including connective, epithelial, hematopoietic, lymphoid, and nervous tissues. Tumor cells exhibit high mitotic and proliferative activity, a shortened cell cycle, and reduced rates of cell death, with continuous growth being the main distinguishing feature from normal cells. Well-differentiated tumors grow slowly, metastasize less frequently, and are less responsive to cytostatic drugs, whereas poorly differentiated tumors proliferate rapidly, metastasize early, and tend to be more sensitive to chemotherapy.

Carcinogenesis (oncogenesis or tumorigenesis) involves the transformation of normal cells into malignant ones through a multistage process that includes initiation, promotion, malignant transformation, progression, local tissue invasion, and metastasis. Initiation involves genetic alterations or mutations resulting from dysregulated biochemical signaling pathways that control proliferation, survival, and differentiation. During promotion, preneoplastic cells with high proliferative activity accumulate, while progression represents the transition from premalignant lesions to invasive cancer, marked by rapid tumor growth, genetic and phenotypic changes, and heightened cell proliferation. Metastasis occurs when cancer cells spread via the bloodstream or lymphatic system from the primary site to distant organs [1].

Key risk factors for cancer development include genetic predisposition, environmental exposures [2], and aging [3]. DNA damage is a primary driver of tumorigenesis, with somatic cell mutations arising from diverse

carcinogenic factors. Genetic and epigenetic alterations determine tumor behavior, including uncontrolled proliferation, tissue invasion, and metastasis. Critical mechanisms in malignant transformation include activation of proto-oncogenes, inactivation of tumor suppressor genes (such as p53 and RAS), and dysregulation of proliferative signaling pathways.

Notable genes associated with cancer include [2]:

- Cell cycle genes: p53 (brain and breast cancers), p16 (melanoma), Rb1 (retinoblastoma), VHL (renal cancer), WT1 (Wilms tumor)
- DNA repair genes: BRCA1/BRCA2 (breast cancer), MLH1, MSH2, MSH6, PMS1, PMS2 (colon cancer), XPA-XPG (skin cancer)
- Signal transduction genes: MET (papillary renal carcinoma), NF1 (neurofibroma), RET (pheochromocytoma)
- Genes regulating tissue organization: APC (colon cancer), E-cadherin (gastric cancer), NF2 (neurinoma)

Endogenous factors can also cause DNA damage. For example, macrophages and neutrophils in inflamed colonic epithelium contribute to colon tumorigenesis through reactive oxygen species, while high-fat diets increase bile acids, promoting DNA damage and colon cancer [3, 4]. Exogenous environmental factors include:

Physical factors

1. Ionizing radiation causing gene mutations or chromosomal aberrations in lung and thyroid cancers
2. UV radiation from sunlight leading to DNA damage in melanoma [5]

Chemical factors

1. Benzo[a]pyrene from tobacco smoke, causing lung cancer via p53 mutations [6, 7]
2. Ethanol, linked to esophageal cancer through p53 alterations [7]
3. Cadmium, associated with prostate cancer [8]
4. Aflatoxin from Aspergillus flavus, causing liver cancer [9]
5. Heterocyclic amines from overcooked meat or fish [10]

Biological factors

1. Helicobacter pylori infection, inducing gastric cancer [11]
2. Hepatitis B or C virus, causing liver cancer
3. Human T-lymphotropic virus type 1, associated with T-cell lymphoma
4. Human papillomavirus, linked to esophageal cancer [1]
5. Chronic bacterial or parasitic infections [12]

Cytotoxic chemotherapy has demonstrated efficacy across various cancers, including lung, pancreatic, and colorectal cancers [13]. Platinum-based compounds are among the most commonly employed cytostatic agents [14]. Clinically approved platinum drugs include Cisplatin, Carboplatin, Oxaliplatin, Nedaplatin (Japan), Lobaplatin (China), Heptaplatin (South Korea), and Satraplatin, which is orally administered [15]. **Tables 1 and 2** summarize the manufacturers and trade names of these approved platinum agents.

Table 1. Manufacturers of approved platinum drugs

Drug	Manufacturers
Cisplatin	Bristol-Myers, National Cancer Institute, Johnson Matthey, Engelhard Industries (USA)
Carboplatin	Bristol-Myers Squibb, Johnson Matthey, Cancer Research Institute, Marsden Royal Hospital (London)
Oxaliplatin	Sanofi-Aventis, Roger Bellon Laboratories, DebioPharm Laboratories, Sanofi-Synthélabo Laboratories
Nedaplatin	Shionogi Pharmaceutical (Osaka, Japan)
Heptaplatin	Sunkyong Industry (SK Chemicals, Kyungki-Do, South Korea)
Lobaplatin	ASTA Medica (Germany), Zentaris AG, Hainan Tianwang (Chang'an) International Pharmaceutical
Satraplatin	Institute for Cancer Research (London), Johnson Matthey, AnorMed

Table 2. Names of approved platinum drugs

Drug	Chemical Name	Other/Trade Name(s)
Cisplatin	cis-diamminedichloroplatinum(II)	CDDP
Carboplatin	cis-diamine-(1,1-cyclobutanedicarboxylate) platinum(II)	Paraplatin, JM 8
Oxaliplatin	1R,2R-diaminocyclohexane oxalate platinum(II)	Eloxatin
Nedaplatin	cis-diamine-glycolato-(O^1,O^2) platinum(II)	254-S
Lobaplatin	cis-(trans-1,2-diaminocyclobutane-lactato) platinum(II)	D-19466
Heptaplatin	cis-malonato-((4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane) platinum(II)	SKI2053R
Satraplatin	bis(acetato)ammine-dichlorocyclohexylamine platinum(IV)	JM 216

The progression of therapeutic development is summarized in **Table 3** for Cisplatin and Carboplatin, and in **Table 4** for the remaining approved derivatives of Cisplatin.

Table 3. Development of the therapy with Cisplatin and Carboplatin

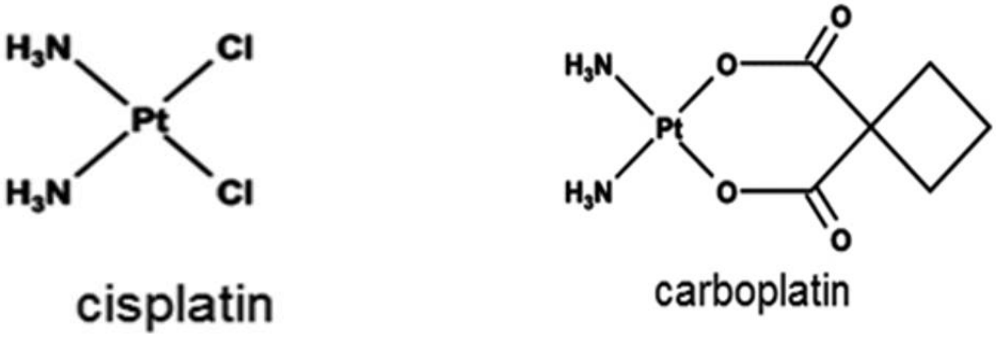
Year	Cisplatin
1845	First synthesis of Cisplatin by Italian chemist Michele Peyrone.
1965	Barnet Rosenberg discovers the biological activity of Cisplatin.
1966	X-ray analysis confirms the cis-geometry of Cisplatin.
1968	Initial demonstration of Cisplatin's antitumor activity in mouse models.
1970	Cisplatin enters clinical trials for non-small cell lung cancer.
1971	First clinical use of Cisplatin in patients.
1975	Phase II clinical trials for Cisplatin commence.
1978	FDA grants approval for Cisplatin.
1978	Platinol receives authorization.
1979	Cisplatin introduced in the United Kingdom.
1979	Platinex approved in Germany.
1985	Various DNA adducts formed by Cisplatin are characterized.
1987	Cisplatin receives authorization in Austria.
1991	Elevated glutathione identified as a factor in tumor resistance to Cisplatin.
1996	Marketing authorization granted for the generic Cisplatin Hospira.
1998	Teva Santé introduces generic Cisplatin in France.
1999	Molecular defect causing hypersensitivity of certain testicular cancers to Cisplatin identified.
2002	CTR1 transporter recognized as key for Cisplatin cellular uptake.
Year	**Carboplatin**
1982	First clinical use of Carboplatin in patients.
1988	Carboplat approved in Germany.
1989	FDA approves Carboplatin for ovarian cancer.
1989	Paraplatin (Bristol-Myers Squibb) introduced by FDA.
1990	Carboplatin approved in the United Kingdom for ovarian carcinoma.
1992	Authorization of Pfizer-developed Carboplatin in France.

1995	Carboplatin introduced in Austria.
2006	FDA approves Bevacizumab in combination with Carboplatin and Paclitaxel for non-small cell lung cancer.

Table 4. Progression of Therapeutic Applications Using Cisplatin Derivatives.

Year	Oxaliplatin [16]
1996	Initial authorization of Oxaliplatin for use as a second-line therapy under the brand name Eloxatin (Sanofi Aventis).
1998	Approval granted for Eloxatin to treat advanced colorectal cancer.
1999	The launch of Eloxatin in key European countries.
1992	Initial clinical trial showing the efficacy of Oxaliplatin combined with 5-Fluorouracil in colorectal cancer patients.
2002	FDA approval of Oxaliplatin for the treatment of colorectal cancer.
2004	Therapeutic regimen combining Oxaliplatin, 5-Fluorouracil, and Leucovorin.
	Nedaplatin [16]
1986	Initially synthesized by Totani *et al*. in Japan [17] .
1998	Authorization of Nedaplatin for clinical use in Japan.
	Lobaplatin [16]
1992	Initiation of clinical trials for Lobaplatin.
	Picoplatin [16]
1997	Initial administration of Picoplatin to patients with small cell lung cancer.
	Satraplatin [16]
1993	First-ever oral administration of Satraplatin to patients.
2007	FDA approval of Satraplatin for treating prostate cancer.

Cisplatin, originally synthesized as Peyrone's chloride by the Italian chemist Michele Peyrone, has become a cornerstone in cancer therapy. The generic form, Hospira, is approved for a wider array of cancers than those listed by the FDA, which include advanced or metastatic testicular, ovarian, and bladder malignancies. Beyond these, Hospira is also used to treat non-small and small cell lung cancer, squamous cell carcinoma of the head and neck, and cervical carcinoma, particularly when administered alongside chemotherapy or radiotherapy. In Germany, Platinex is authorized for testicular, ovarian, and bladder cancers. Carboplatin's approved applications cover epithelial ovarian cancer, small cell lung carcinoma, squamous cell carcinoma of the head and neck, and metastatic ovarian and cervical cancers. In Austria, Carboplatin is additionally indicated for bladder cancer, cervical carcinoma, non-small cell lung cancer, and squamous cell carcinoma of the head and neck [16]. The molecular structures of these platinum-based drugs are presented in **Figure 1, and Table 6** summarizes their key pharmacokinetic properties.



a) b)

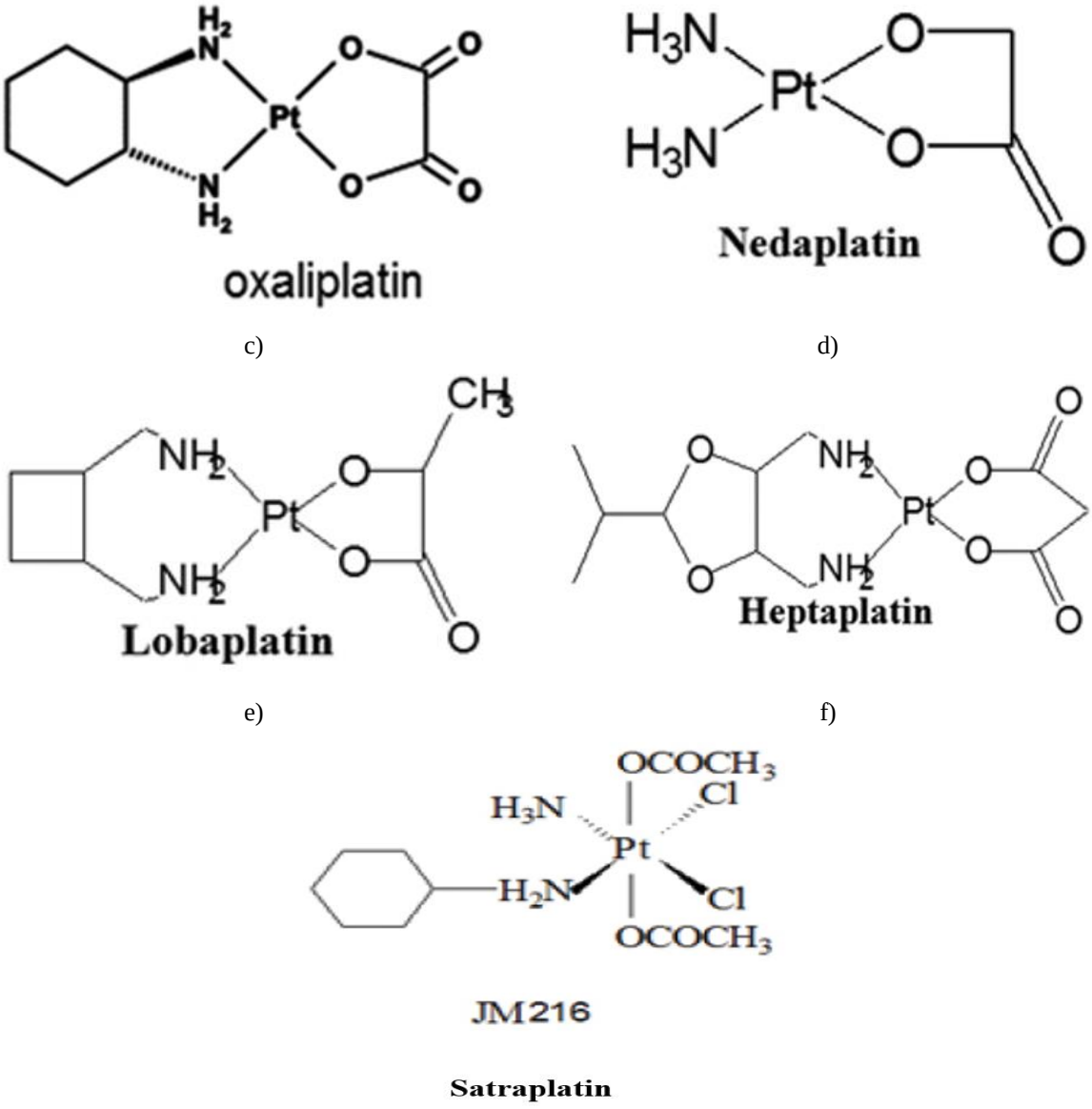


Figure 1. Chemical structures of approved platinum drugs.

Table 6. The most importamnt pharmacokinetic parameters for approved platinum drugs.

Pharmacokinetic parameters	Cisplatin	Carboplatin [18]	Oxaliplatin	Nedaplatin
Bioavailability	100%	100%	15%	good
Distribution volume	11–12 l	16 l	440 l	12 l
Protein binding	> 95%	low [19]	> 90%	50%
Elimination half-life	30–100 h	2.6–5.9 h	10–25 min	-
Excretion	renal	renal	renal	renal

Cisplatin exhibits extensive binding to plasma proteins, including gamma-globulin, albumin, and transferrin, with approximately 90% of plasma platinum bound two hours after a three-hour infusion. Tissue concentrations are highest in the liver, kidneys, and prostate, while lower levels are observed in muscle, pancreas, spleen, and bladder, and the lowest levels are detected in the brain, cerebellum, lungs, heart, and adrenal glands. Platinum persists in tissues for up to six months following the final dose. Complexes formed between Cisplatin and albumin remain largely stable and are cleared slowly, with a minimum elimination half-life of five days or longer.

Carboplatin shows a distribution half-life of 1.1–2 hours and is primarily excreted unchanged via the urine, with 65% eliminated within 12 hours, 71% within 24 hours, and an additional 5% between 24 and 96 hours, without significant biliary excretion. Following a 30-minute intravenous infusion at 500 mg/m², total body clearance is 4.4 L/h [20]. Oxaliplatin binds mainly to albumin and gamma-globulins in plasma and also forms irreversible bonds with erythrocytes. At the conclusion of a two-hour infusion, only 15% of the administered platinum remains in circulation, while 85% is rapidly distributed into tissues or eliminated via urine in a triphasic manner, with half-lives of t½ α = 0.43 h, t½ β = 16.8 h, and t½ γ = 391 h [21]. Nedaplatin is predominantly excreted renally, accounting for 59.6% of the administered dose [22, 23].

Table 7 summarizes the approved clinical indications for these platinum-based agents.

Table 7. Indications for approved platinum drugs

Drug	Indications
Cisplatin	Ovarian [24] , testicular [25], esophageal [26], gastric, colon, pancreatic, hepatic, renal, and prostatic cancers [27]; bladder [28] ; breast [29] ; small cell and non-small cell lung cancer [30]; glioblastoma, head and neck squamous cell carcinoma, refractory non-Hodgkin's lymphoma, sarcoma [28] ; peritoneal and pleural mesothelioma, neuroblastoma, metastatic melanoma, leukemia [31]
Carboplatin	Cancers of the ovary, cervix, testicles, brain, bladder, breast, head and neck, lungs; also retinoblastoma, neuroblastoma, nephroblastoma [32]
Oxaliplatin	Ovarian, breast, head and neck cancers; non-Hodgkin's lymphoma, malignant melanoma, glioblastoma, non-small cell lung cancer (NSCLC), and neuroendocrine tumors [33]
Nedaplatin	Head and neck, esophageal, small cell lung, NSCLC, ovarian, testicular, prostate, and cervical cancers [34, 35]
Heptaplatin	Gastric cancer (Hong *et al.* 1996); small cell lung cancer [36, 37]
Lobaplatin	Chronic myelocytic leukemia, small cell lung, breast, gastric cancers; esophageal squamous cell carcinoma, hypopharyngeal carcinoma, osteosarcoma [38-40]
Satraplatin	Lung, breast, cervical, prostate, and ovarian cancers [41]

The clinical trial results are summarized in **Table 8** for Cisplatin, Carboplatin, and Lobaplatin, and in **Table 9** for Oxaliplatin, Nedaplatin, and Satraplatin.

Table 8. Clinical trials for Cisplatin, Carboplatin, and Lobaplatin

Drug	Clinical Trial Indications
Cisplatin (https://go.drugbank.com/drugs/DB00515) [42]	**Cancers:** Brain; Head and Neck; Hypopharyngeal; Laryngeal; Oropharyngeal; Small Cell Lung; Non-Small Cell Lung; Breast; Peritoneal Cavity; Liver; Bladder; Cervical; Endometrial; Extragonadal; Prostate **Adenocarcinomas:** Lung; Esophageal; Gastroesophageal; Stomach; Pancreatic; Cervical; Endometrial **Carcinomas:** Head and Neck; Salivary Gland; Tongue; Esophageal Squamous Cell; Hypopharyngeal; Laryngeal; Nasopharyngeal; Oropharyngeal; Non-Small Cell Lung; Lung Squamous; Squamous Cell; Bladder; Biliary Tract; Urothelial; Cervical; Ovarian; Adrenocortical; Intrahepatic Cholangiocarcinoma **Neoplasms:** Brain; Head and Neck; Esophageal; Nasopharyngeal; Gastric; Pancreas; Testicular **Lymphomas:** Nasal; Peripheral T Cell; Hodgkin **Blastomas:** Hepatoblastoma; Medulloblastoma **Other:** Melanoma; Mesothelioma; Nasopharyngeal Lymphoepithelioma; Sarcoma

Carboplatin (https://go.drugbank.com/drugs/DB00958) [43]	**Cancers:** Brain; Neuroendocrine; Head and Neck; Small Cell Lung; Non-Small Cell Lung; Breast; Gastroesophageal; Peritoneal; Cervical; Ovarian; Endometrial; Extragonadal; Embryonal **Carcinomas:** Neuroendocrine; Esophageal; Non-Small Cell Lung; Lung Squamous; Squamous Cell; Colorectal; Urothelial; Hepatocellular; Cervical **Neoplasms:** Esophageal; Lung; Breast; Abdominal Wall; Cervical; Ovarian **Lymphomas:** Non-Hodgkin's **Blastomas:** Neuroblastoma; Medulloblastoma; Retinoblastoma **Other:** Lung Adenocarcinoma; Mesothelioma
Lobaplatin (https://go.drugbank.com/drugs/DB13049) [44]	**Cancers:** Small Cell Lung; Breast **Carcinomas:** Head and Neck; Esophageal; Nasopharyngeal; Hepatocellular **Neoplasm:** Stomach **Other:** Osteosarcoma

Table 9. Clinical trials for Oxaliplatin, Nedaplatin, and Satraplatin

Drug	Clinical Trial Indications
Oxaliplatin (https://go.drugbank.com/drugs/DB00526) [45]	**Adenocarcinomas:** Esophageal; Gastroesophageal; Gastric; Pancreatic; Colorectal; Bowel; Cervical **Cancers:** Brain; Breast; Esophageal; Gastric; Gastroesophageal; Pancreatic; Peritoneal; Colon; Colorectal; Biliary Tract; Liver; Cervical; Ovarian; Prostate **Carcinomas:** Neuroendocrine; Non-Small Cell Lung; Esophageal; Gastroesophageal; Pancreatic; Peritoneal; Colorectal; Rectal; Hepatocellular; Cervical; Ovarian **Neoplasms:** Esophageal; Nasopharyngeal; Breast; Gastrointestinal; Pancreatic; Colorectal; Hepatic; Biliary Tract **Lymphomas:** Non-Hodgkin's; Nasal; NK-T Cell; B-Cell **Blastomas:** Hepatoblastoma
Nedaplatin (https://go.drugbank.com/drugs/DB13145) [46]	**Cancers:** Small Cell Lung; Gastric; Ovarian; Cervical **Carcinomas:** Head and Neck; Esophageal; Nasopharyngeal; Non-Small Cell Lung **Neoplasms:** Esophageal
Satraplatin (https://go.drugbank.com/drugs/DB04996S) [47]	**Cancers:** Breast; Lung; Prostate **Carcinomas:** Non-Small Cell Lung **Neoplasms:** Brain

Neurotoxicity represents the primary adverse effect associated with Cisplatin treatment, affecting approximately 47% of patients. Clinical manifestations include numbness, tingling, paresthesia in the extremities, impaired gait, and reduced tendon reflex sensitivity. This neuropathy is often persistent, with symptoms typically worsening during the first four months of therapy and potentially lasting up to 52 months after discontinuation. The severity of peripheral neuropathy corresponds to the higher accumulation of Cisplatin in peripheral nervous system tissues, such as peripheral nerves and dorsal root ganglia, compared with central nervous system tissues like the brain and spinal cord.

The toxicity profiles of platinum-based drugs are summarized in **Table 10** [48].

Table 10. Toxicity of approved platinum drugs [48, 49]

Drug	Common Side Effects	Dose-Limiting Toxicity
Cisplatin	Nausea, vomiting, electrolyte imbalances including hypomagnesemia, hypokalemia, hypocalcemia; hemolytic anemia [50]	Neurotoxicity, hearing impairment, paresthesia, sensory ataxia [50, 51]; nephrotoxicity [52-54]; ototoxicity [55]; myelosuppression [50]
Carboplatin	Neuropathy; nephrotoxicity, ototoxicity, gastrointestinal disturbances [50]	Myelosuppression including thrombocytopenia, neutropenia, leukopenia [50]
Oxaliplatin	Neutropenia, fatigue, nausea, vomiting, diarrhea, ototoxicity [56]; hypokalemia [57]	Neurotoxicity [58, 59]
Nedaplatin	Nephrotoxicity, neurotoxicity, gastrointestinal toxicity [35]	Myelosuppression including thrombocytopenia, neutropenia, leukopenia, anemia

Heptaplatin	Leukopenia, thrombocytopenia, neurotoxicity, hepatotoxicity, embryotoxicity [60]	Nephrotoxicity [61]
Satraplatin	Granulocytopenia, anemia, diarrhea, constipation, nausea, vomiting [50]	Thrombocytopenia, leukopenia, neutropenia

Recent advances in antitumor coordination chemistry [62, 63] have focused on synthesizing cytotoxic metal complexes of platinum, palladium, and gold coordinated with porphyrin ligands [64], including hematoporphyrin IX derivatives such as monomeric platinum (III) [65], paramagnetic platinum [66], palladium (III) [67], and gold (II) complexes [68]; platinum complexes engineered for alternative DNA interactions and tumor-selective cytotoxicity [69]; as well as platinum (IV) compounds including Enthacraplatin, Iproplatin, Mitaplatin, Ormaplatin (Tetraplatin), and Satraplatin [70].

Conclusion

Over 1000 clinical trials have been documented for Cisplatin, Carboplatin, and Oxaliplatin, with Cisplatin being the most extensively studied. In contrast, newer agents such as Lobaplatin, Nedaplatin, and Satraplatin have undergone relatively few trials, approximately ten per drug. Distinct dose-limiting toxicities have been observed among these drugs: Cisplatin primarily causes neurotoxicity, nephrotoxicity, and ototoxicity; Oxaliplatin is associated with neurotoxicity; Heptaplatin mainly exhibits nephrotoxicity; and Carboplatin, Nedaplatin, and Satraplatin are linked to myelosuppressive effects, including thrombocytopenia, neutropenia, and leukopenia.

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