

Comparative assessment of clinical trials, indications, pharmacokinetic parameters and side effects of approved platinum drugs

Stefka Ivanova¹

¹ Department of Pharmaceutical Chemistry and Pharmacognosy, Faculty of Pharmacy Medical University-Pleven, Kliment Ohridski str. 1, 5800, Pleven, Bulgaria

Corresponding author: Stefka Ivanova (ivanovastefka_pharm@yahoo.com)

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Abstract

Platinum complexes are among the most commonly applied anticancer agents. The aim of current work is collection, analysing and comparative estimation of clinical trials and pharmacological indications of currently approved for application platinum derivatives: Cisplatin, Carboplatin, Oxaliplatin, Nedaplatin (Japan), Lobaplatin (China), Heptaplatin (North Korea), and Satraplatin. The other aim of the study includes the summarizing of the historic data for the stages of the development of these drugs, and the comparison of pharmacokinetic parameters, side effects and the dose-limiting factors of the drugs. The observational study on pharmacokinetic parameters shows that protein binding decreases in order: 95% (Cisplatin); 90% (Oxaliplatin); 50% (Nedaplatin); low (Carboplatin). For every of Cisplatin, Carboplatin, Oxaliplatin have been reported more than 1000 clinical trials; for Lobaplatin, Nedaplatin, Satraplatin - about 10 trials. The differences in dose-limiting effects are: neuro-, nephro-, ototoxicity (Cisplatin); neurotoxicity (Oxaliplatin); nephrotoxicity (Heptaplatin); myelosuppression: thrombocytopenia, neutropenia, leukopenia (Carboplatin, Nedaplatin, Satraplatin).

Keywords

application, Cisplatin derivatives, limiting factors

Introduction

Malignant tumors are the leading cause of lethality worldwide, and are a group of more than 100 different types of diseases, that are characterized by uncontrolled cell growth, local tissue invasion and distant metastases. The incidence of malignant tumors is enlarging, with the fastest increasing of lung, prostate, and colon cancers in men and breast carcinomas in women. Malignant tumors originate from different types of tissues: connective, epithelial, hematopoietic, lymphoid, nervous. Tumor cells are characterized by high mitotic and proliferative activity,

have a shorter cell cycle duration, and a lower rate of cell death. The main difference between a normal and a tumor cell is the continuous tumor growth. Highly differentiated tumors have slower growth, metastasize relatively less frequently and later, and are less sensitive to cytostatics. Poorly differentiated cells proliferate rapidly, metastasize to distant organs, and are sensitive to cytostatics.

In carcinogenesis (oncogenesis, tumorigenesis) normal cells are transformed into cancer cells. This multistage process involves changes at the cellular and genetic levels, and involves initiation, promotion, malignant formation, progression, local tissue invasion and metastases. Initiation is

characterized with the alteration, change, or mutation of genes. Genetic alterations are result from dysregulation of biochemical signaling pathways, associated with cellular proliferation, survival, and differentiation. The actively proliferating preneoplastic cells accumulate in the promotion stage. Progression is the final stage of neoplastic transformation, and is the phase between a premalignant lesion and the development of invasive cancer. Fast increase in the tumor size, genetic and phenotypic changes, and cell proliferation occur in progression phase. Metastasis is the spread of cancer cells through the bloodstream or the lymph system, from the primary site to other parts of the body (Siddiqui et al. 2015).

The most significant risk factor for the development of cancer are genetic and environmental factors (Saeki and SugiIchi 2001) and old age (Anisimov et al. 2009). DNA damage is considered to be the primary cause of cancer. At the molecular level, tumors are considered a mutation in somatic cell DNA, caused by various carcinogenic factors. In this process, various genetic and epigenetic tumor-specific mutations occur, which define the biological features of tumor growth: uncontrolled cell proliferation, invasion of neighboring tissues and metastasis of cells to distant tissues. The main reasons for the transformation of a normal cell into a malignant one are: conversion of proto-oncogenes into oncogenes, inactivation of tumor suppressor genes (p53, RAS), and dysregulation of positive and negative signals for proliferation.

Genetic abnormalities include the following genes (Saeki and SugiIchi 2001):

- I. cell cycle genes: p53 (brain and breast cancer); p16 (melanoma); Rb1 (retinoblastoma); VHL (renal cancer); WT1 (Wilms cancer)
- II. DNA repair genes: BRCA1, BRCA2 (breast cancer); MLH1, MSH2, MSH6, PMS1, PMS2 (colon cancer); XPA, XPB, XPC, XPD, XPF, XPG (skin cancer)
- III. signal transduction genes: MET (papillary renal cell carcinoma); NF1 (neurofibroma); RET (adrenal pheochromocytoma)
- IV. genes responsible for tissue organization: APC (colon cancer); E-cadherin (gastric cancer); NF2 (neurinoma).

DNA damage can also be caused by substances, produced in the body. Macrophages and neutrophils in an inflamed colonic epithelium initiate colonic tumorigenesis (Anisimov VN et al. 2009), due to the DNA damage by reactive oxygen species. In high-fat diet, high levels of bile acids cause DNA damage, and contribute to colon cancer (Bernstein et al. 2011).

DNA damage can arise too from exposure to exogenous environmental carcinogenic agents:

- I. Physical factors
 - 1 ionized radiation: gene mutation or chromosome aberration in lung and thyroid cancer
 - 2 UV-light from solar radiation: DNA damage in melanoma (Kanavy and Gerstenblith 2011)
- II. Chemical factors

- 1 benzo-pyrene: from tobacco smoke (Kuper et al. 2002): lung cancer, due to mutation in the p53 gene, a tumor suppressor gene, which is considered to be one of the mechanisms of carcinogenesis (Saeki et al. 2000)
- 2 ethyl alcohol: esophageal cancer, due to p53 gene abnormalities (Saeki et al. 2000)
- 3 cadmium: prostate cancer. (Irigaray et al. 2007)
- 4 *Aspergillus flavus* metabolite aflatoxin: liver cancer (Smela et al. 2002)
- 5 heterocyclic amines: overcooked meat and fish (de Verdier et al. 1991)

III. Biological factors

- 1 *Helicobacter pylori* infection: produces gastric cancer (Handa et al. 2011)
- 2 Hepatitis B virus or Hepatitis C virus: liver cancer.
- 3 Human T-lymphotrophic virus type 1: T cell lymphoma
- 4 Human papilloma virus: esophagus cancer (Siddiqui et al. 2015), chronic bacterial and parasitic infections (Samaras et al. 2010).

Cytotoxic chemotherapy has proven useful in a number of different cancer types including: lung, pancreatic and colorectal ca Cancer (Corrie 2008). One of the most commonly used cytostatics are platinum complexes (Wheate et al. 2010).

Currently used in clinical practice: worldwide Cisplatin, Carboplatin, Oxaliplatin, Nedaplatin (registered in Japan), Lobaplatin (approved in China), Heptaplatin (South Korea), Satraplatin - for oral administration (Ndagi et al. 2020).

In the following tables are summarized producers (Table 1.) and names (Table 2.) of approved platinum drugs.

The development of the therapy is presented in Table 3. (Cisplatin and Carboplatin) and in Table 4. (other approved Cisplatin derivatives).

Table 1. Manufacturers of approved platinum drugs.

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

Table 2. Names of approved platinum drugs.

| Drug | Chemca name | Additional name |
|-------------|--|------------------|
| Cisplatin | cisdiamminedichloroplatinum II | CDDP |
| Carboplatin | cis-diamine-(1,1-cyclobutanedicarboxylate) Pt II | Paraplatin, JM 8 |
| Oxaliplatin | 1R,2R-diaminocyclohexane oxalate Pt II | Eloxatin |
| Nedaplatin | cis-diamine-glycolate-O ¹ ,O ³ Pt II | 254-S |
| Lobaplatin | cis-(trans-1,2-diaminocyclobutane-lactato) Pt II | D-19466 |
| Heptaplatin | cis-malonato((4R,5R)-4,5-bis (aminomethyl)-2-isopropyl-1,3-dioxo-lane) Pt II | SKI2053R |
| Satraplatin | bis(acetato)amminedichlorocyclohexylamine Pt IV | JM 216 |

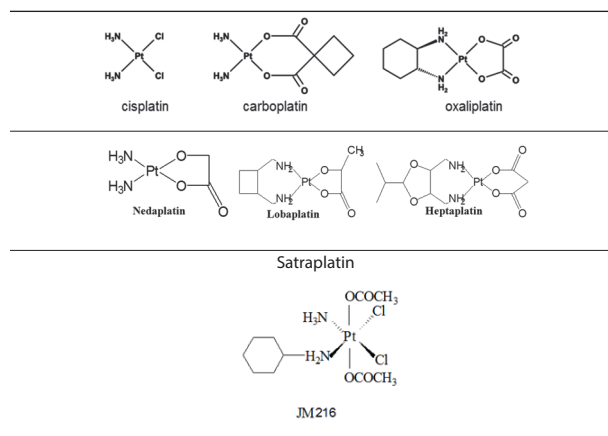
Table 3. Development of the therapy with Cisplatin and Carboplatin.

| Year | Cisplatin |
|-------------|--|
| 1845 | The earliest preparation of Cisplatin by the Italian chemist Michele Peyrone. |
| 1965 | Discovering of biological activity of Cisplatin by Barnet Rosenberg |
| 1966 | Confirmation of cis-geometry of Cisplatin by an X-ray method. |
| 1968 | The earliest pproved activity of Cisplatin against model mice tumors. |
| 1970 | Cisplatin enters clinical trial in non-small cell lung cancer. |
| 1971 | The earliest application of Cisplatin in patients. |
| 1975 | The beginning of Phase II clinical trials for Cisplatin. |
| 1978 | The approval of Cisplatin by the Food and Drug Administration. |
| 1978 | The authorisation of Platinol. |
| 1979 | The intraduction for Cisplatin in the United Kingdom. |
| 1979 | The approval for Platinex in Germany. |
| 1985 | Description of various cisplatin-induced adducts formed on DNA. |
| 1987 | The authorisation for Cisplatin in Austria. |
| 1991 | Role of elevated glutathione in inducing tumor resistance to Cisplatin. |
| 1996 | The generic Cisplatin Hospira receives marketing authorisation. |
| 1998 | The intraduction for Cisplatin as generic product of Teva Sante in France. |
| 1999 | Identification of the molecular defect that causes hypersensitivity of some testicular cancers to Cisplatin. |
| 2002 | Identification of the role of the CTR1 in transporting Cisplatin into cells. |
| Carboplatin | |
| 1982 | The earliest application of Carboplatin in patients. |
| 1988 | The approval of Carboplat in Germany. |
| 1989 | The authorisation of Carboplatin by FDA (ovarian cancer). |
| 1989 | The introduction from FDA of Paraplatin (Bristol-Myers Squibb) |
| 1990 | The approval of Carboplatin in the United Kingdom for ovarian carcinoma. |
| 1992 | The authorisation in France of Carboplatin, developed by Pfizer. |
| 1995 | The introduction of Carboplatin in Austria. |
| 2006 | FDA regulatory approval of Bevacizumab for the treatment of non-small cell lung cancer in combination with Carboplatin and Paclitaxel. |

Table 4. Development of the therapy with Cisplatin derivatives.

| Year | Oxaliplatin (Kalayda 2020) |
|----------------------------|--|
| 1996 | Firstly approval for the second-line treatment of Oxaliplatin under the trade name Eloxatin (Sanofi Aventis). |
| 1998 | The authorisation of Eloxatin for advanced colorectal cancer. |
| 1999 | The introduction of Eloxatin iu major Europe states. |
| 1992 | First clinical study, demonstrating the effect of Oxaliplatin in combination with 5-Fluorouracil in patients with colorectal cancer. |
| 2002 | Oxaliplatin FDA regulatory approval for use in the treatment of colorectal cancer. |
| 2004 | Combination therapy: Oxaliplatin, 5-Fluorouracil and Leucovorin |
| Nedaplatin (Kalayda 2020) | |
| 1986 | Firstly prepared by Totani et al. in Japan (Totani et al. 1986) |
| 1998 | The approval of Nedaplatin for clinical application in Japan. |
| Lobaplatin (Kalayda 2020) | |
| 1992 | The introduction of Lobaplatin into clinical trials. |
| Picoplatin (Kalayda 2020) | |
| 1997 | The earliest Picoplatin administration in patients with small cell lung cancer. |
| Satraplatin (Kalayda 2020) | |
| 1993 | Oral administration for the first time of Satraplatin to patients. |
| 2007 | Satraplatin FDA regulatory approval for the treatment of prostate cancer. |

Cisplatin as Peyrone's chloride has been prepared by the Italian chemist Michele Peyrone For the generic Cisplatin Hospira, the approved indication spectrum is wider than that authorised by FDA (advanced or metastatic testicular, ovarian and bladder cancer), and includes: non-small and small cell lung carcinoma, squamous cell carcinoma of the head and neck, and cervical carcinoma, when combined with chemo- or radiotherapy. In Germany Platinex has been approved on for treatment of testicular, ovarian, and bladder cancer. The indication spectrum for Carboplat is for epithelial ovarian cancer, small cell lung carcinoma, squamous carcinoma of the head and neck, and metastatic

Table 5. Chemical structures of approved platinum drugs.**Table 6.** The most important pharmacokinetic parameters for approved platinum drugs.

| Pharmacokinetic parameters | Cisplatin | Carboplatin (Oguri et al. 1988) | Oxaliplatin | Nedaplatin |
|----------------------------|-----------|-----------------------------------|-------------|------------|
| Bioavailability | 100% | 100% | 15% | good |
| Distribution volume | 11–12 l | 16 l | 440 l | 12 l |
| Protein binding | > 95% | low (Sooriyaarachchi et al. 2011) | > 90% | 50% |
| Elimination half-life | 30–100 h | 2.6–5.9 h | 10–25 min | - |
| Excretion | renal | renal | renal | renal |

cervical and ovarian cancer. In Austria Carboplatin indications includes: bladder cancer, squamous carcinoma of the head and neck, non-small cell lung cancer, and cervical carcinoma (Kalayda 2020).

The chemical structures of approved platinum drugs are illustrated on Table 5., and in Table 6. are summarized the most important pharmacokinetic parameters.

Cisplatin is binding to plasma proteins: gammaglobulin, albumin, transferrin, and 90% of the plasma platinum is protein-bound 2 h after 3 h infusion. Cisplatin concentrations are highest in liver, kidney, prostate; lower in muscle, pancreas, spleen, bladder, and lowest in cerebrum, cerebellum, lung, heart, adrenal. In tissues platinum is present 6 months after the last administration. The complexes between albumin and Cisplatin do not dissociate to a significant extent, and are eliminated slowly with a minimum half-life of 5 days or more.

The distribution half-life of Carboplatin is 1.1–2 h. Predominantly the drug is eliminated in the urine as the unchanged parent compound: 65% within 12 h, 71% within 24 h; 5% from 24 h to 96 h, without biliary elimination. The total body clearance after a 30 min. intravenous infusion of 500 mg/m² is 4.4 l/h (Reece et al. 1987). Oxaliplatin plasma protein binding is primarily to albumin and gammaglobulins. The drug also irreversibly binds to erythrocytes. At the end of a 2 h infusion of Oxaliplatin, 15% of the administered platinum is present in the systemic circulation, and 85% is rapidly distributed into tissues or eliminated triphasic in the urine – $t_{1/2\alpha} = 0.43$ h, $t_{1/2\beta} = 16.8$ h, $t_{1/2\gamma} = 391$ h (Levi et al. 2000). The excretion of Nedaplatin is renal (59.6%) (Sasaki et al. 1989; Ishibashi et al. 2003).

The indications for the approved platinum drugs are presented in Table 7.

Table 7. Indications for approved platinum drugs.

| Drug | Indications |
|-------------|--|
| Cisplatin | ovarian (Meng et al. 2013), testicles (Dhar et al. 2011), esophagus (Koizumi et al. 2008), stomach, colon, pancreas, liver, kidney, prostate (Desoize and Madoulet 2002), bladder (Dasari and Tchounwou 2014), breast (Decatris et al. 2004), small cell lung, non-small cell lung (Minami et al. 2013), gastric (Koizumi et al. 2008) cancers, malignant brain glioblastoma, head and neck squamous cell carcinoma, refractory non-Hodgkin's lymphoma and sarcoma (Dasari and Tchounwou 2014), peritoneal and pleural mesothelioma, neuroblastoma, metastatic melanoma, leukemia (Previati et al. 2006) |
| Carboplatin | ovarian, cervical, testicular, brain, bladder, breast, head, neck and lung cancers, retinoblastoma, neuroblastoma, nephroblastoma (de Sousa et al. 2014) |
| Oxaliplatin | ovarian, breast, head and neck cancer, non-Hodgkin's lymphoma, malignant melanoma, glioblastoma, NSCLC, neuroendocrine tumors (Spada et al. 2016) |
| Nedaplatin | head, neck, esophagus, small cell lung, non-small cell lung cancer, ovarian, testicular, prostate, cervical cancer (Koshiyama et al. 2005; Shimada et al. 2013) |
| Heptaplatin | gastric (Hong et al. 1996), small cell lung cancer (Hong et al. 1995; Zang et al. 1999) |
| Lobaplatin | chronic myelocytic leukemia, small-cell lung, breast, gastric cancer, esophageal squamous cell and hypopharyngeal carcinoma, osteosarcoma (Gienema et al. 1993; Degardin et al. 1995; Wu et al. 2018) |
| Satraplatin | lung, breast, cervical, prostate and ovarian cancer (Bhargava and Vaishampayan 2009) |

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

| Cisplatin (https://go.drugbank.com/drugs/DB00515) | |
|---|--|
| 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 |
| Lymphoms | Nasal; Peripheral T Cell; Hodgkin |
| Blastomas | Hepatoblastoma; Medulloblastoma |
| Other | Melanoma; Mesothelioma; Nasopharyngeal Lymphoepithelioma; Sarcoma |
| Carboplatin (https://go.drugbank.com/drugs/DB00958) | |
| 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 |
| Lymphoms | Non-Hodgkin's |
| Blastomas | Neuroblastoma; Medulloblastoma; Retinoblastoma |
| Other | Lung adenocarcinoma; Mesothelioma |
| Lobaplatin (https://go.drugbank.com/drugs/DB13049) | |
| Cancer | Small Cell Lung; Breast |
| Carcinoma | Head and neck; Esophageal; Nasopharyngeal; Hepatocellular |
| Neoplasm | Stomach |
| Other | Osteosarcoma |

The data for the clinical trials are shown on Table 8. (Cisplatin, Carboplatin, Lobaplatin) and on Table 9. (Oxaliplatin, Nedaplatin, Satraplatin).

Neurotoxicity is the most important adverse effect of Cisplatin chemotherapy in 47% of patients. Symptoms include numbness, tingling, paraesthesia in the limbs, difficulty walking, decreased sensation of tendon reflexes. Neuropathy is long-term with significant worsening of symptoms during the first 4 months, which may continue 52 months after stopping treatment. Higher concentrations in peripheral nervous system tissues (peripheral nerves and dorsal root ganglia), compared to central nervous

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

| Oxaliplatin (https://go.drugbank.com/drugs/DB00526) | |
|---|--|
| Adeno-carcinoma | Esophageal; Gastroesophageal; Gastric; Pancreas; Colorectal; Bowel; Cervix |
| 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 |
| Lymphoms | Non-Hodgkin's; Nasal; NK-T-Cell; B-Cell |
| Blastomas | Hepatoblastoma |
| Nedaplatin (https://go.drugbank.com/drugs/DB13145) | |
| Cancers | Small Cell Lung; Gastric; Ovarian; Cervical |
| Carcinoma | Head and Neck; Esophageal; Nasopharyngeal; Non-Small Cell Lung |
| Neoplasms | Esophageal |
| Satraplatin (https://go.drugbank.com/drugs/DB04996S) | |
| Cancers | Breast Lung Prostate |
| Carcinoma | Non-Small Cell Lung |
| Neoplasms | Brain |

Table 10. Toxicity of approved platinum drugs (Markman 2003; Hartmann and Lipp 2003).

| Drug | Side-effects | Dose-limiting side effects |
|-------------|--|--|
| Cisplatin | nausea, vomiting, electrolyte disturbance: hypomagnesaemia, hypokalaemia and hypocalcaemia, hemolytic anemia (Oun et al. 2018) | neurotoxicity, hearing disorder, paraesthesia, sensory ataxia (Avan et al. 2015; Oun et al. 2018), nephrotoxicity (Yao et al. 2007; Pabla and Dong 2008; Miller et al. 2010), ototoxicity (Waissbluth and Daniel 2013), myelosuppression (Oun et al. 2018) |
| Carboplatin | neuropathy, nephro-, oto- and gastrointestinal toxicity (Oun et al. 2018) | myelosuppression: thrombocytopenia, neutropenia, leukopenia (Oun et al. 2018) |
| Oxaliplatin | neutropenia, ototoxicity, fatigue, nausea, vomiting, diarrhea (Cassidy and Misset 2002), hypokalemia (Chay et al. 2010) | neurotoxicity (Argyriou et al. 2008; Gebremedhn et al. 2018) |
| Nedaplatin | nephro-, neuro-, gastrointestinal toxicity (Shimada et al. 2013) | myelosuppression: thrombocytopenia, neutropenia, leucopenia, anemia |
| Heptaplatin | leukopenia, thrombocytopenia, neurohepato-, embryotoxicity (Chung et al. 1988) | nephrotoxicity (Ahn et al. 2008) |
| Satraplatin | granulocytopenia, anemia, diarrhea, constipation, nausea, vomiting (Oun et al. 2018) | thrombocytopenia, leucopenia, neutropenia |

system tissues (brain, spinal cord) correlate with clinical symptoms of peripheral neuropathy.

Toxicity of platinum compounds is presented on Table 10 (Hartmann and Lipp 2003).

Recent developments in antitumor coordination compounds (Momekov and Momekova 2006; Shaili 2014) is synthesis of cytotoxic platinum, palladium and gold metal complexes with porphyrin ligands (Doneva et al. 2014), as hematoporphyrin IX complexes: monomeric platinum (III) (Momekov et al. 2010), paramagnetic platinum (Gencheva et al. 2007), palladium III (Momekov et al. 2018), and gold II complexes (Momekov et al. 2008); platinum complexes with an alternative DNA-binding and tumor-targeted cytotoxicity (Momekov et al. 2005); platinum (IV) agents: Enthacraplatin, Iproplatin, Mitaplatin, Ormaplatin (Tetraplatin), Satraplatin (Monneret 2011).

Conclusion

More than 1000 clinical trials have been reported for every of the following anticancer agents: Cisplatin, Carboplatin, Oxaliplatin. The more investigations have been applied for Cisplatin. In comparison, for Lobaplatin, Nedaplatin, and Satraplatin have been reported very few clinical trials – about 10 for every drug. The following differences in dose-limiting effects have been reported: neuro-, nephro-

and ototoxicity (Cisplatin); neurotoxicity (Oxaliplatin); nephrotoxicity (Heptaplatin); myelosuppression: thrombocytopenia, neutropenia and leukopenia (Carboplatin, Nedaplatin, Satraplatin).

Conflict of interests

There are no conflict of interests.

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