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ADVERSE DRUG REACTIONS INDUCED BY CISPLATIN IN CANCER PATIENTS: A COMPREHENSIVE REVIEW

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Abstract

Cisplatin is a widely used chemotherapy drug that has greatly improved cancer treatment outcomes. However, its effectiveness is hindered by the occurrence of adverse drug reactions (ADRs) in cancer patients. This comprehensive review aims to extensively examine the ADRs caused by cisplatin in patients with cancer. The review initially discusses the mechanisms of how cisplatin works and how it is processed in the body (pharmacokinetics). It then thoroughly explores the various types of ADRs associated with cisplatin, which include kidney toxicity, hearing loss, neurological issues, cardiotoxicity, hepatotoxicity, and others. The review delves into the underlying mechanisms and risk factors that contribute to the development of these ADRs. The use of combination therapies involving cisplatin and other drugs has been extensively explored as a promising approach to address drug resistance and minimize toxicity. The review concludes by highlighting the importance of individualized patient monitoring and proactive management of ADRs to optimize the therapeutic benefits of cisplatin while minimizing its associated toxicity.

Keywords: Adverse drug reaction, oncology, toxicity, chemotherapy.

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INTRODUCTION:

Cisplatin, a commonly used chemotherapeutic agent, has significantly contributed to the treatment of various cancers. However, its clinical utility is often hampered by the occurrence of adverse drug reactions (ADRs) in patients. ADRs are unwanted and potentially harmful effects that result from the administration of a medication. Cisplatin-induced ADRs can range from mild to severe and may impact various organ systems, including the kidneys, ears, nervous system, hepatotoxicity, cardiotoxicity, and others. These ADRs not only affect patient well-being but can also lead to treatment delays, dose reductions, or discontinuation, thus compromising the effectiveness of cancer therapy. Understanding the nature, mechanisms, and management of cisplatin induced ADRs is crucial for healthcare professionals involved in the care of cancer patients[1]. This review aims to provide an overview of the adverse drug reactions associated with cisplatin, highlighting their clinical significance, underlying mechanisms, risk factors, and potential management strategies. By enhancing our knowledge and awareness of cisplatin-induced ADRs, we can optimize patient care and treatment outcomes in the context of cisplatin-based chemotherapy[1-2]. Cisplatin, also known as cisplatinum or cis-diamminedichloroplatinum(II) (CDDP), is a chemotherapy drug derived from platinum. It is extensively used in the treatment of various cancers, including sarcomas, certain carcinomas like small cell lung cancer and ovarian cancer, lymphomas, and germ cell tumours. Cisplatin belongs to a class of alkylating agents, which are named for their ability to add alkyl groups to certain molecules in cells[4].

Its primary mode of action involves cross-linking the guanine bases within DNA strands, effectively disrupting the DNA structure, and preventing the replication and separation necessary for cell division. This leads to a halt in tumour growth. Additionally, cisplatin can add alkyl groups to molecules, such as methyl groups, where they don't belong. This interference inhibits the proper utilization of these molecules through base pairing, resulting in DNA miscoding. The cumulative effect of these mechanisms is the disruption of DNA function and eventual cell death. It is important to note that alkylating agents like cisplatin are not specific to any phase of the cell cycle, meaning they can act on cells in different phases. These agents work through various mechanisms to achieve the same outcome of DNA damage and cell death[3-5].

CISPLATIN AND ITS GROUP OF DRUGS:

Cisplatin belongs to a group of drugs known as platinum-based chemotherapy agents. This group of drugs includes other platinum compounds that are used in cancer treatment.

Carboplatin: Carboplatin is a platinum-containing chemotherapy drug similar to cisplatin. It is often used as an alternative to cisplatin, particularly in cases where renal toxicity is a concern. Carboplatin is commonly used in the treatment of ovarian cancer, lung cancer, and other malignancies[6].

Oxaliplatin: Oxaliplatin is another platinum-based chemotherapy drug used to treat various types of cancer, including colorectal cancer. It is often used in combination with other chemotherapy agents, such as fluorouracil and leucovorin, in the treatment of advanced or metastatic colorectal cancer[6].

Nedaplatin: Nedaplatin is a platinum-containing chemotherapy drug used primarily in the treatment of testicular cancer and various types of solid tumours, including lung, head and neck, and bladder cancers. It is structurally related to cisplatin and carboplatin[5].

Satraplatin: Satraplatin is an oral platinum-based chemotherapy drug used in the

treatment of advanced prostate cancer. It is administered orally, making it a convenient option for patients.

Lobaplatin: Lobaplatin is a platinum-containing chemotherapy drug used mainly in the treatment of lung, ovarian, and other gynaecological cancers. It is like cisplatin and carboplatin but has a modified structure[6].

USES OF CISPLATIN FOR ONCOLOGY PATIENT:

Lung cancer:

Lung cancer remains a prevalent and deadly form of cancer, with small cell lung cancer (SCLC) representing 15% of all cases. Platinum-based treatments are currently the cornerstone of SCLC chemotherapy, with cisplatin and carboplatin being the most commonly used drugs in this class. Cisplatin is frequently chosen in clinical trials due to its potent antitumor activity, but it is associated with adverse effects such as renal toxicity, nausea, and vomiting. To mitigate renal toxicity, monitoring urine volumes and administering large-dose infusions are essential during cisplatin-based chemotherapy. In clinical practice, carboplatin has been considered as an alternative to cisplatin without a significant loss of therapeutic efficacy, especially when aggressive hydration poses challenges. For localized non-small-cell lung cancer (NSCLC), the current standard of care involves surgical intervention followed by adjuvant cisplatin-based chemotherapy, particularly for stage II and III disease. The Lung Adjuvant Cisplatin Evaluation program, which conducted a pooled analysis of the five largest trials, recently demonstrated a 5.3% absolute 5-year survival benefit with adjuvant chemotherapy. Similarly, a meta-analysis of NSCLC studies also supported the use of adjuvant chemotherapy. CD133, a glycoprotein found on the surface of organ-specific stem cells, has been identified as a marker for cancer-initiating cells in various tumour types. In primary NSCLC, it has been observed that a population expressing both CD133 and epithelial-specific antigen (CD133+ESA+) is elevated compared to normal lung tissue[4-7].

Ovarian cancer:

Ovarian cancer is the most lethal among gynaecologic cancers, often diagnosed at advanced stages due to a lack of effective screening methods and specific early-stage symptoms. The standard treatment for advanced ovarian cancer involves surgical removal of the tumour followed by a combination of platinum and taxane chemotherapy. While this initial treatment approach is effective, recurrence rates in ovarian cancer patients can be as high as 75%. With time, patients with recurrent ovarian cancer develop resistance to chemotherapy, leading to a poor prognosis. Most ovarian cancers, approximately 90%, originate from the ovaries with an unknown aetiology.[7-9] The remaining cases may have a hereditary component or be associated with breast and colon cancers. Despite the severe side effects and the development of resistance, cisplatin derivatives remain the primary treatment option for ovarian cancer. They are used either alone or in combination with other chemical agents or compounds to target both resistant and sensitive ovarian cancer cell lines[8].

Carcinoma:

Head and neck squamous cell carcinoma (HNSCC) are a prevalent malignancy, with over 600,000 new cases reported worldwide each year. Despite advancements in treatment modalities such as surgery, radiation, and chemotherapy, HNSCC remains associated with a significant mortality rate[10]. The overall 5-year survival rate has remained stagnant at approximately 50% over the past few decades. Cisplatin as a standalone drug is not effective in the treatment of this disease. A randomized study comparing the efficacy of cisplatin alone versus its combination with methotrexate, vinblastine, doxorubicin, or gemcitabine has been

conducted in patients with metastatic urothelial carcinoma[11].

Breast cancer:

Breast cancer remains a significant cause of mortality among women worldwide. Currently, chemotherapy is the primary treatment option for malignant breast cancer, as it helps to extend the lifespan of patients[13]. The development of chemotherapeutic agents has been crucial in addressing the ongoing challenges posed by breast cancer. However, many of these agents are classified as "cytotoxic drugs" because they primarily target rapidly dividing cells, leading to cellular damage. Among these drugs, cisplatin plays a crucial role as a widely used chemotherapeutic agent for various malignancies, including breast, testicular, ovarian, cervical, prostate, head and neck, bladder, lung, and refractory non-Hodgkin's lymphomas. The cytotoxic effects of cisplatin are believed to occur through the formation of cisplatin-DNA adducts, which inhibit DNA replication and ultimately induce apoptosis[14].

Brain cancer:

Glioblastoma multiforme is the most prevalent primary malignant brain tumor and is almost always fatal, except for rare cases. The current standard treatment approach for GBMs involves a combination of surgery, radiotherapy, and temozolomide chemotherapy. Following this treatment regimen, repetitive cycles of temozolomide are administered. Although this combined approach has shown a survival benefit at the 5-year mark, the overall increase in median survival is only around 2.5 months. Cisplatin therapy is also utilized for recurrent brain tumours in children and is employed in the treatment of various other cancers, including gastric cancer, anal cancer, and leukaemia[12-14].

CISPLATIN WITH OTHER CANCER DRUGS:

Cisplatin combination chemotherapy serves as the cornerstone of treatment for various types of cancers. While many cancer patients initially respond well to platinum-based therapy, a significant number will eventually experience relapse with cisplatin-resistant disease. This development of drug resistance has been observed in patients who have relapsed from cisplatin treatment. Proposed mechanisms underlying cisplatin resistance involve alterations in cellular uptake and efflux of cisplatin, increased biotransformation, and detoxification processes in the liver, as well as enhanced DNA repair and anti-apoptotic mechanisms. To address this issue of resistance, cisplatin is frequently employed in combination with other drugs in the treatment of several cancer types. This combination approach is used to target ovarian cancer, biliary tract cancer, lung cancer, gastric cancer, carcinoma of salivary gland origin, breast cancer, colon cancer, lung cancer, prostate cancer, melanoma, pancreatic cancer cell lines, squamous cell carcinoma of the male genital tract, urothelial bladder cancer, and cervical cancer. By combining cisplatin with other drugs, researchers aim to enhance treatment efficacy and overcome cisplatin resistance in these malignancies[15-16].

Cisplatin and Paclitaxel:

A combination chemotherapy regimen comprising of paclitaxel, cisplatin, and fluorouracil has demonstrated effectiveness and tolerability as both first line and second-line therapy in Chinese patients with advanced gastric and esophagogastric junction adenocarcinoma. Studies have indicated that this treatment approach exhibits improved tolerability and has shown promising results in clinical outcomes[14].

Cisplatin and Tegafur-uracil:

The combination of oral UFT and cisplatin has been demonstrated as an efficacious treatment regimen for advanced non-small cell lung carcinoma. Studies have indicated that this combination chemotherapy

approach is effective in treating the disease and has shown positive outcomes in clinical trials[13].

Cisplatin and Doxorubicin:

The combination chemotherapy consisting of cyclophosphamide, doxorubicin, and cisplatin has demonstrated promising outcomes in the treatment of advanced carcinomas originating from the salivary glands. Clinical studies have reported encouraging results for this combination chemotherapy regimen in managing the disease[12].

Cisplatin and Gemcitabine:

The combination of cisplatin and gemcitabine is a suitable choice for treating individuals diagnosed with advanced biliary cancer. This chemotherapy regimen has been identified as an appropriate option in the management of patients with this specific type of cancer[16].

ADVERSE DRUG REACTION OF CISPLATIN:

Neurotoxicity:

Peripheral neurotoxicity is the primary limiting factor in the administration of cisplatin due to its dose-dependent nature. Various mechanisms have been proposed to explain the development of neurotoxicity, suggesting that cisplatin induces apoptosis in both malignant cells and peripheral neurons. Approximately 50% of patients receiving cisplatin experience peripheral neurotoxicity, but its onset is typically observed after cumulative doses exceeding 300 mg/m2[3]. Symptoms primarily affect the upper and lower extremities and include sensory impairments such as loss of vibration and position senses, tingling sensations, muscle weakness, tremors, and taste disturbances. In rare cases, seizures and leukoencephalopathy have also been reported. While discontinuation of cisplatin treatment may lead to gradual improvement of neurological function, the effects can persist or become permanent over time[14-15].

Hepatotoxicity:

Excessive doses of cisplatin can result in liver toxicity, characterized by oxidative stress as a primary mechanism. This oxidative stress may be attributed to a decrease in reduced glutathione (GSH) levels, as observed in various studies on rats treated with cisplatin[6-9]. These studies have also reported a notable increase in hepatic malondialdehyde (MDA) levels, indicating lipid peroxidation, along with a reduction in the activity of antioxidant enzymes. Hepatic transaminases are highly sensitive biomarkers that reflect cellular damage and toxicity, as they are released into the bloodstream following cellular injury. Elevated levels of hepatic enzymes and bilirubin serve as indicators of impaired liver function. Cisplatin-induced hepatotoxicity can be exacerbated by an upregulation of cytochrome P450-2E1 enzyme expression. Histopathological examination typically reveals hepatocyte necrosis and degeneration, accompanied by infiltration of inflammatory cells around the portal area and sinusoidal dilatation. Recent studies have focused on protective strategies against cisplatin-induced hepatotoxicity, including the use of agents such as selenium and vitamin E[18-20].

Ototoxicity:

Cisplatin has been found to have ototoxic effects, causing tinnitus (ringing in the ears) and hearing loss in a significant number of patients. Up to 31% of patients treated with an initial intravenous dose of cisplatin at 50 mg/m2 have experienced these symptoms. Additionally, when a higher dose of 150 mg/m2 was administered, about 30% of patients showed temporary hearing loss and mild abnormalities in their audiometric tests. The mechanisms underlying cisplatin-induced damage to the cochlea's outer hair cells likely involve the generation of reactive oxygen radicals and depletion of glutathione. Several risk factors contribute to the susceptibility of ototoxicity, including the simultaneous use of other

potentially harmful agents (such as aminoglycosides), prior cranial irradiation, pre-existing renal dysfunction, or existing damage to the inner ear[19-20].

Cardiotoxicity:

Resulting from cisplatin administration can lead to the release of lactate dehydrogenase (LDH) and creatine kinase (CK) from cardiac myocytes. This phenomenon is thought to occur as a secondary event following cisplatin-induced lipid peroxidation of cardiac membranes. Histological changes associated with cisplatin-induced cardiotoxicity include degeneration and necrosis of cardiac muscle fibres, along with the presence of fibrous tissue reaction. Furthermore, many muscle cells exhibit vacuolated cytoplasm, and blood vessels show signs of dilation with an increased blood volume[13-15].

Nephrotoxicity:

Cisplatin is known to accumulate more prominently in the kidneys compared to other organs, primarily due to its preferential uptake and excretion by renal tissues. The concentration of cisplatin within the proximal tubular epithelial cells of the kidneys can be approximately five times higher than its concentration in the bloodstream. This disproportionate accumulation in kidney tissue significantly contributes to the development of nephrotoxicity induced by cisplatin[7]. The synthesis of the amino acids lysine and methionine results in the production of a quaternary ammonium compound called Carnitine. Carnitine plays a crucial role in transporting fatty acids from the cytosol into the mitochondria during the breakdown of lipids to generate metabolic energy. The inhibition of Carnitine synthesis, as well as impaired reabsorption of Carnitine by the proximal tubule of the nephron, contribute to kidney damage caused by cisplatin. This can lead to a decline in Carnitine production, affecting its availability for essential cellular processes[19-20].

Clearance of cisplatin from the body occurs through both glomerular filtration and tubular secretion in the kidneys[5]. Interestingly, cisplatin concentrations within the kidney surpass those found in the bloodstream, suggesting an active accumulation of the drug by renal parenchymal cells. Recent studies have identified two specific membrane transporters, namely Ctr1 and OCT2, that play a role in transporting cisplatin into cells. Furthermore, within the kidney, cisplatin undergoes biotransformation into cysteinyl glycine conjugates and other high thiols through the activity of localized enzymes[18-20].

Other organs:

Additional toxicities associated with cisplatin treatment include gastrotoxicity (damage to the gastrointestinal system), myelosuppression (reduction in bone marrow activity), allergic reactions, and potential reproductive toxicity. These adverse effects have been documented in studies investigating the effects of cisplatin on various organs and physiological systems[6,20].

CONCLUSION:

In conclusion, cisplatin, a widely used chemotherapy drug, is associated with various organ toxicities. Neurotoxicity is a significant dose-limiting factor, affecting peripheral nerves and presenting with sensory impairments and motor dysfunction. Hepatotoxicity may occur due to oxidative stress and disruption of liver function, leading to cellular damage and inflammation. Ototoxicity, characterized by tinnitus and hearing loss, is attributed to oxidative damage and depletion of protective factors in the cochlea. Cardiotoxicity can result in cardiac cell

damage and fibrosis, while nephrotoxicity arises from cisplatin accumulation in renal tissues, affecting kidney function and Carnitine synthesis. These toxicities emphasize the need for close monitoring and protective strategies during cisplatin treatment. Other organs, such as the gastrointestinal system, bone marrow, and reproductive organs, may also experience adverse effects. Overall, understanding the mechanisms and risks associated with cisplatin-induced organ toxicities can guide efforts to mitigate their impact and improve patient outcomes.

REFERENCE:

1. Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. Mol Cancer Ther. 2003 May;2(5):471-8. PMID: 12748309.
2. Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A Systematic Review of Strategies to Prevent Cisplatin-Induced Nephrotoxicity. Oncologist. 2017 May;22(5):609-619. doi: 10.1634/theoncologist.2016-0319. Epub 2017 Apr 24. PMID: 28438887; PMCID: PMC5423518.
3. Aggarwal SK. A histochemical approach to the mechanism of action of cisplatin and its analogues. J Histochem Cytochem. 1993 Jul;41(7):1053-73. doi: 10.1177/41.7.8515048. PMID: 8515048.
4. Arts HJ, Hollema H, Lemstra W, Willemse PH, De Vries EG, Kampinga HH, Van der Zee AG. Heat-shock-protein-27 (hsp27) expression in ovarian carcinoma: relation in response to chemotherapy and prognosis. Int J Cancer. 1999 Jun 21;84(3):234-8. doi: 10.1002/(sici)1097-0215(19990621)84:3<234::aid-ijc6>3.0.co;2-9. PMID: 10371339.
5. Baniahmad A, Tsai MJ. Mechanisms of transcriptional activation by steroid hormone receptors. J Cell Biochem. 1993 Feb;51(2):151-6. doi: 10.1002/jcb.240510206. PMID: 8440749.
6. Basu A, Krishnamurthy S. Cellular responses to Cisplatin-induced DNA damage. J Nucleic Acids. 2010 Aug 8;2010:201367. doi: 10.4061/2010/201367. PMID: 20811617; PMCID: PMC2929606.
7. Beck DJ, Brubaker RR. Effect of cis-platinum(II)diamminodichloride on wild type and deoxyribonucleic acid repair deficient mutants of Escherichia coli. J Bacteriol. 1973 Dec;116(3):1247-52. doi: 10.1128/jb.116.3.1247-1252.1973. PMID: 4584807; PMCID: PMC246480.
8. Belfi CA, Chatterjee S, Gosky DM, Berger SJ, Berger NA. Increased sensitivity of human colon cancer cells to DNA cross-linking agents after GRP78 up-regulation. Biochem Biophys Res Commun. 1999 Apr 13;257(2):361-8. doi: 10.1006/bbrc.1999.0472. PMID: 10198218.
9. Brazil DP, Hemmings BA. Ten years of protein kinase B signalling: a hard Akt to follow. Trends Biochem Sci. 2001 Nov;26(11):657-64. doi: 10.1016/s0968-0004(01)01958-2. PMID: 11701324.
10. Brozovic A, Ambriović-Ristov A, Osmak M. The relationship between cisplatin-induced reactive oxygen species, glutathione, and BCL-2 and resistance to cisplatin. Crit Rev Toxicol. 2010 Apr;40(4):347-59. doi: 10.3109/10408441003601836. PMID: 20163198.
11. Brozovic A, Simaga S, Osmak M. Induction of heat shock protein 70 in drug-resistant cells by anticancer drugs and hyperthermia. Neoplasma. 2001;48(2):99-103. PMID: 11478701.
12. Byun JM, Jeong DH, Lee DS, Kim JR, Park SG, Kang MS, Kim YN, Lee KB, Sung MS, Kim KT. Tetraarsenic oxide and cisplatin induce apoptotic synergism in cervical cancer. Oncol Rep. 2013

Apr;29(4):1540-6. doi: 10.3892/or.2013.2243. Epub 2013 Jan 18. PMID: 23338680.
13. Chian S, Li YY, Wang XJ, Tang XW. Luteolin sensitizes two oxaliplatin-resistant colorectal cancer cell lines to chemotherapeutic drugs via inhibition of the Nrf2 pathway. Asian Pac J Cancer Prev. 2014;15(6):2911-6. doi: 10.7314/apjcp.2014.15.6.2911. PMID: 24761924.
14. Chen G, Huynh M, Fehrenbacher L, West H, Lara PN Jr, Yavorkovsky LL, Russin M, Goldstein D, Gandara D, Lau D. Phase II trial of irinotecan and carboplatin for extensive or relapsed small-cell lung cancer. J Clin Oncol. 2009 Mar 20;27(9):1401-4. doi: 10.1200/JCO.2008.20.2127. Epub 2009 Feb 9. PMID: 19204194; PMCID: PMC2668551.
15. Cho JM, Manandhar S, Lee HR, Park HM, Kwak MK. Role of the Nrf2-antioxidant system in cytotoxicity mediated by anticancer cisplatin: implication to cancer cell resistance. Cancer Lett. 2008 Feb 18;260(1-2):96-108. doi: 10.1016/j.canlet.2007.10.022. Epub 2007 Nov 26. PMID: 18036733.
16. Colombo N, Sessa C, Landoni F, Sartori E, Pecorelli S, Mangioni C. Cisplatin, vinblastine, and bleomycin combination chemotherapy in metastatic granulosa cell tumor of the ovary. Obstet Gynecol. 1986 Feb;67(2):265-8. doi: 10.1097/00006250-198602000-00020. PMID: 2418394.
17. Creagan ET, Woods JE, Schutt AJ, O'Fallon JR. Cyclophosphamide, adriamycin, and cis-diamminedichloroplatinum (II) in the treatment of advanced nonsquamous cell head and neck cancer. Cancer. 1983 Dec 1;52(11):2007-10. doi: 10.1002/1097-0142(19831201)52:11<2007::aid-cncr2820521106>3.0.co;2-t. PMID: 6684986.
18. Cuadrado A, Lafarga V, Cheung PC, Dolado I, Llanos S, Cohen P, Nebreda AR. A new p38 MAP kinase-regulated transcriptional coactivator that stimulates p53-dependent apoptosis. EMBO J. 2007 Apr 18;26(8):2115-26. doi: 10.1038/sj.emboj.7601657. Epub 2007 Mar 22. PMID: 17380123; PMCID: PMC1852783.
19. Decatris MP, Sundar S, O'Byrne KJ. Platinum-based chemotherapy in metastatic breast cancer: current status. Cancer Treat Rev. 2004 Feb;30(1):53-81. doi: 10.1016/S0305-7372(03)00139-7. PMID: 14766126.
20. Saad SY, Najjar TA, Alashari M. Role of non-selective adenosine receptor blockade and phosphodiesterase inhibition in cisplatin-induced nephrogonadal toxicity in rats. Clin Exp Pharmacol Physiol. 2004 Dec;31(12):862-7. doi: 10.1111/j.1440-1681.2004.04127.x. PMID: 15659050.