Optic neuritis, papilledema and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin therapy. Steroids with or without mannitol have been used, however efficacy of the same has not been established. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended in the package insert. Altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis and often the only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic like reactions have been occasionally reported in patients previously exposed to cisplatin and these consist of facial edema, wheezing, tachycardia and hypotension within minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteriods and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic like reactions and supportive equipment and medication should be available to treat such a complication.

Transient elevation in liver enzymes, especially SGOT, as well as bilirubin may be associated with cisplatin administration at the recommended doses. Infrequently cardiac abnormalities, hiccups, elevated serum amylase and rashes may be seen. Alopecia, malaise and asthenia have been testified in postmarketing surveillance reports. Local soft tissue toxicity has rarely been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/ml may result in tissue cellulitis, fibrosis and necrosis.

WARNING(S)

Cisplatin produces cumulative nephrotoxicity potentiated by aminoglycoside antibiotics; serum creatinine, BUN, creatinine clearance, magnesium, sodium, potassium and calcium levels should be measured prior to initiating therapy and prior to each subsequent course. It is highly recommended that cisplatin should not be given more frequently than once every 3-4 weeks. Elderly patients may be more susceptible to nephrotoxicity and peripheral neuropathy. Severe neuropathies may be seen in patients in whom regimens are employed using higher doses of cisplatin or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking glove distribution, areflexia, loss of proprioception and vibratory sensation.

Loss of motor function has also been reported. Anaphylactic like reactions to cisplatin may occur within minutes of administration to patients with prior exposure to cisplatin and have been alleviated by administration of epinephrine, corticosteriods and antihistamines. Ototoxicity of cisplatin is cumulative hence audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug.

Cisplatin can cause fetal harm when administered to pregnant women. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice cisplatin is teratogenic and embryotoxic; thus it is highly advised that if cisplatin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant when on cisplatin therapy.

The development of acute leukemia coincident with the use of cisplatin has rarely been reported in humans when given in combination with other leukemogenic agents. For optimal benefits it is important to receive each scheduled dose of this medication as directed, however if a dose is missed it is advisable to visit the treating doctor to establish a new dosing schedule.

PRECAUTION(S)

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly.

Pregnancy Category D

Nursing Mothers - cisplatin has been reported to be found in human milk hence patients receiving cisplatin should not breast feed.

Pediatric use - the safety and effectiveness in pediatric patients have not been established.

Geriatric use - insufficient data is available on cisplatin in the treatment of metastatic testicular tumors or advanced bladder cancer to determine whether elderly patients respond differently than younger patients. Higher incidences of severe thrombocytopenia and leukopenia have been reported in elderly compared with younger patients. Elderly patients in general have a numerically higher incidence of peripheral neuropathy than younger patients. Clinical reports suggest that elderly patients may be more susceptible to myelosuppression, infectious complications and nephrotoxicity than younger patients. Cisplatin is known to be substantially excreted by the kidney and is contraindicated in patients with pre-existing renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored.

DRUG INTERACTION(S)

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy. Reports suggest that in advanced ovarian cancer the response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin

OVERDOSAGE(S)

Caution should be exercised to prevent inadvertent overdosage with CISWEL™. Acute overdosage with cisplatin may result in kidney failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, intractable nausea, vomiting and/or neuritis. Death can occur following overdosage. No proven antidotes have been established for cisplatin overdosage. Hemodialysis, even when initiated four hours after the overdosage, appears to have little effect on removing platinum from the body because of cisplatin's rapid and high degree of protein binding. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that may occur.

STORAGE

Cisplatin injection is a sterile, single dose vial without preservatives. Store between 15-25 °C (59-77 °F). Do not refrigerate. Protect unopened container from light. Cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light. Cisplatin and fluorouracil admixtures are stable in 0.9 % normal saline for 1 h.

PRESENTATION

CISWEL™ is supplied in single dose amber glass vial containing 1 mg/ml of cisplatin as 10 mg/10 ml and/or 50 mg/50 ml.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines have been published on proper handling and disposal of anticancer drugs however there is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing CISWEL™. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. It is advisable not to flush medications down the toilet or pour them into a drain unless instructed to do so. Properly discard this product on expiry or when no longer needed.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by:
Getwell Pharmaceuticals
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0700DPC

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Cisplatin Injection BP

CISWEL™

Antineoplastic Agent

FOR I.V INFUSION AFTER DILUTION

Rx only

WARNING

CISWEL™ should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Cumulative renal toxicity associated with cisplatin is often severe. Other major dose related toxicities are myelosuppression, nausea and vomiting.

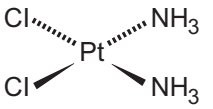
Ototoxicity which may be more pronounced in children is manifested by tinnitus and/or loss of high frequency hearing and occasionally deafness is significant.

Anaphylactic like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of cisplatin administration. Epinephrine, corticosteriods, and antihistamines have been effectively employed to alleviate symptoms.

Caution must be exercised to prevent inadvertent CISWEL™ overdose. It is not advisable to use doses greater than 100 mg/m^2/cycle once every 3-4 weeks. Care must be taken to avoid inadvertent CISWEL™ overdose due to confusion with carboplatin or prescribing practices that fail to differentiate daily doses from total dose per cycle.

DESCRIPTION

Cisplatin or *cis*-diamminedichloroplatinum(II) (CDDP) is a platinum based chemotherapy drug used to treat various types of cancers including sarcomas, some carcinomas (e.g. small cell lung cancer and ovarian cancer), lymphomas and germ cell tumors. Cisplatin is the first member of a class of anti-cancer drugs which also includes carboplatin and oxaliplatin. Cisplatin injection is a sterile aqueous solution, available in 50 and 10 ml single dose vials where each ml contains 1 mg of cisplatin and 9 mg sodium chloride in sterile water for injection. HCl and/or sodium hydroxide may be added to adjust the pH to 3.5-4.5. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. Cisplatin is a yellow powder or yellow or orange-yellow crystals with the molecular formula $PtCl_2H_6N_2$ and a molecular weight of 300.05. It is soluble in water or saline at 1 mg/ml and in dimethylformamide at 24 mg/ml. Cispaltin has a melting point of 207 °C.



The synthesis of cisplatin is a classic in inorganic chemistry. Starting from potassium tetrachloroplatinate(II) ($K_2[PtCl_4]$), the first NH_3 ligand is added to any of the four equivalent positions but the second NH_3 could be added cis or trans to the bound ammine ligand. However because Cl^- has a larger trans effect than NH_3, the second ammine preferentially substitutes trans to a chloride ligand and therefore cis to the original ammine. Since the trans effect of halides follows the order $I^- > Br^- > Cl^-$, therefore the synthesis of cisplatin is conducted using $[PtI_4]^{2-}$ to ensure high yield and purity of the cis isomer followed by conversion of the $PtI_2(NH_3)_2$ into $PtCl_2(NH_3)_2$.

COMPOSITION

Each ml contains	
Cisplatin IP	1 mg
Sodium Chloride IP	9 mg
Hydrochloric Acid IP (To adjust pH)	q.s
Water for Injection IP	q.s

CLINICAL PHARMACOLOGY & MECHANISM OF ACTION

Following administration of cisplatin, one of the chloride ligands is slowly displaced by water (an aqua ligand), in a process termed aquation. The aqua ligand in the resulting $[PtCl(H_2O)(NH_3)_2]^+$ is itself easily displaced, allowing the platinum atom to coordinate to a basic site in DNA. Subsequently crosslinking of two DNA bases occurs via displacement of the other chloride ligand. Cisplatin forms crosslinks with DNA in several ways, interfering with cell division by mitosis. The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis when repair proves impossible. It has been shown that apoptosis induced by cisplatin on human colon cancer cells depends on the mitochondrial serine-protease Omi/$Htra_2$ but it remains an open question if the Omi/$Htra_2$ protein participates in the cisplatin induced apoptosis in carcinomas from other tissues.

Most notable among the DNA changes are the 1, 2 intrastrand cross-links with purine bases including 1, 2 intrastrand d(GpG) adducts which form nearly 90 % of the adducts and the less common 1, 2 intrastrand d(ApG) adducts. 1, 3 intrastrand d(GpXpG) adducts occur but are readily excised by the nucleotide excision repair (NER). Other adducts include inter-strand crosslinks and nonfunctional adducts that have been postulated to contribute to cisplatin's activity. Interaction with cellular proteins, particularly HMG domain proteins, has also been advanced as a mechanism of interfering with mitosis, although this is probably not its primary method of action. Although cisplatin is frequently designated as an alkylating agent, it has no alkyl group and cannot carry out alkylating reactions hence it is correctly classified as alkylating like agent.

Cisplatin resistance: Combination chemotherapy with cisplatin is the cornerstone of treatment of many cancers. Initial platinum responsiveness is high but it has been seen that majority of cancer patients eventually relapse with cisplatin resistant disease. Many mechanisms of cisplatin resistance have been proposed including changes in cellular and increased DNA repair. It has been shown in laboratory studies that oxaliplatin is and increased DNA repair. It has been shown in laboratory studies that oxaliplatin is uptake and efflux of the drug, increased detoxification of the drug, inhibition of apoptosis active in highly cisplatin resistant cancer cells, however there is little evidence for its activity in the clinical treatment of patients with cisplatin resistant cancer. Reports suggest that paclitaxel may be useful in the treatment of cisplatin resistant cancer however the mechanism for this activity is unknown.

PHARMACOKINETICS & PHARMACODYNAMICS

Cisplatin has a volume of distribution of about 11-12 L/m^2 at steady state. Platinum is 90 % protein bound. Cisplatin is excreted in breast milk. The t½ of cisplatin is about 20-30 min and at least

5 days for the platinum albumin complexes. Cisplatin has a clearance (Cl) of about 15-16 L/h/m^2. Renal clearance is estimated to be between 50-62 ml/min/m^2. Cisplatin is 90 % excreted in urine and less than 10 % removed by biliary excretion. Transplatin is the trans stereoisomer of cisplatin, has the formula trans-[$PtCl_2(NH_3)_2$] and does not exhibit a comparably useful pharmacological effect. Its low activity is generally thought to be due to rapid deactivation before it arrives at the DNA. Transplatin is toxic and hence it is desirable to test batches of cisplatin for the absence of the trans isomer.

Plasma concentrations of the parent compound, cisplatin, decays monoexponentially with a ½ life of about 20-30 minutes following bolus administration of 50 or 100 mg/m^2 dose. Monoexponential decay and plasma 1/2 life of about 0.5 hour are also seen following 2 or 7 hour infusions of 100 mg/m^2. After 7 hour infusion the total body clearance and volume of distribution at steady state for cisplatin are about 15-16 L/h/m^2 and 11-12 L/m^2. Due to the unique chemical structure, the chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles such as water or sulfhydryl groups than to enzyme catalyzed metabolism. At physiological pH in the presence of 0.1M NaCl the predominant molecular species are cisplatin and monohydroxymonochloro cis-diammine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by sulfhydryl groups of amino acids or proteins accounts for the instability of cisplatin in biological matrices. The ratio of cisplatin to total free (ultrafilterable) platinum in the plasma varies considerably between patients and ranges from 0.5-1.1 after a 100 mg/m^2 dose.

Cisplatin does not undergo instantaneous and reversible binding to plasma proteins that is characteristic of normal drug protein binding. However platinum from cisplatin, but not cisplatin itself becomes bound to several plasma proteins including albumin, transterrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three hour infusion 90 % of the plasma platinum is protein bound. The complex between albumin and platinum from cisplatin do not dissociate to a significant extent and is slowly eliminated with a minimum ½ life of five days or more.

Following cisplatin dose of 20-120 mg/m^2, the concentrations of platinum is highest in liver, prostate and kidney but somewhat lower in bladder, muscle, testicle, pancreas and spleen the lowest being in the bowel, adrenal, heart, lung, cerebrum and cerebellum. Platinum may be present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentration in tumors is generally somewhat lower than the concentrations in the organ where the tumor is located. Different metastatic sites in the same patient may have different platinum concentrations. Hepatic metastases have the highest platinum concentrations but these are similar to platinum concentrations in normal liver. Maximum red blood cell concentration of platinum is reached within 90-150 minutes after a 100 mg/m^2 dose of cisplatin and declines in a biphasic manner with a terminal 1/2 of 36-47 days.

As much as 10-40 % of the administered platinum is excreted in the urine in 24 hours when 40 to 140 mg/m^2 of cisplatin is administered as a bolus injection or as an infusion varying from 1-24 hours. Over five days following administration of 40-100 mg/m^2 doses given as rapid 2-3 hour or 6-8 hour infusions a mean of 35-51 % of the dosed platinum is excreted in the urine. Reports suggest that 14-30 % is the mean urinary recoveries of platinum for five daily dose administrations of 20, 30 or 40 mg/m^2/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. Platinum containing species excreted in the urine are the same as those found following the incubation of cisplatin with urine from healthy subjects, except that the proportions are different.

The parent compound cisplatin is excreted in the urine and accounts for 13-17 % of the dose excreted within one hour after administration of 50 mg/m^2. The mean renal cisplatin clearance of 62 ml/min/m^2 exceeds creatinine clearance of 50 ml/min/m^2 following administration of 100 mg/m^2 as 2 hour or 6-7 hour infusion. The renal clearance of free (ultrafilterable) platinum also exceeds glomerular filtration rate indicating that cisplatin or other platinum containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear, variable while active secretion of possible tubular reabsorption is dependent on dose, urine flow rate and individual variability.

There is a potential for accumulation of ultrafilterable platinum plasma concentrations whenever cisplatin is administered on a daily basis but not when dosed on an intermittent basis. No significant relationships exist between the renal clearance of either free platinum or cisplatin and creatinine clearance. Although small amounts of platinum are present in the bile and large intestine after administration of cisplatin, the fecal excretion of platinum appears to be insignificant.

INDICATION(S)

CISWEL™ is indicated as therapy for

Metastatic testicular tumors - in established combination therapy with other approved chemotherapeutic agents in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Metastatic ovarian tumors - in established combination therapy with other approved chemotherapeutic agents in patients who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of cisplatin and cyclophosphamide. CISWEL™, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received cisplatin therapy.

Advanced bladder cancer - as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy

DOSAGE & ADMINISTRATION

Note: Needles or intravenous sets containing aluminum parts that may come in contact with CISWEL™ should not be used for preparation or administration. Aluminum reacts with CISWEL™, causing precipitate formation and a loss of potency.

The usual CISWEL™ dose for the treatment of ***testicular cancer*** in combination with other approved chemotherapeutic agents is 20 mg/m^2 I.V daily for 5 days per cycle. The usual CISWEL™ dose for the treatment of ***metastatic ovarian tumors*** in combination with cyclophosphamide is 75-100 mg/m^2 I.V per cycle once every four weeks (day 1). The dose of cyclophosphamide when used in combination with cisplatin is 600 mg/m^2 I.V once every four weeks (day 1). In combination therapy, CISWEL™ and cyclophosphamide are administered sequentially but as a single agent, CISWEL™ should be administered at a dose of 100 mg/m^2 I.V per cycle once every four weeks.

In patients with ***advanced bladder cancer*** CISWEL™ should be administered as a single agent at 50-70 mg/m^2 I.V per cycle once every 3-4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m^2 per cycle repeated every four weeks is recommended.

It is recommended that all patients are to undergo pretreatment hydration with 1-2 liters of fluid infused for 8-12 hours prior to cisplatin dose. CISWEL™ is then required to be diluted in 2 liters of 5 % dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol and infused over a 6-8 hour period. If the diluted solution is not used within 6 hours protect the solution from light. It is not advisable to dilute cisplatin in just 5 % dextrose injection. Adequate hydration and urinary output must be maintained during the following 24 hours after treatment. The course of cisplatin should not be repeated until serum creatinine is below 1.5 mg/100 ml and/or the BUN is below 25 mg/100 ml. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets ≥100,000/mm^3,WBC ≥4,000/mm^3). Subsequent doses of CISWEL™ should not be given until an audiometric analysis indicates that auditory acuity is within normal limits. As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If CISWEL™ contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water. The aqueous solution should be used intravenously only and should be administered by I.V infusion over a 6-8 hour period.

Note: Exercise caution to prevent inadvertent CISWEL™ overdosage. It is advisable to call the prescriber if dose is greater than 100 mg/m^2 per cycle. Additionally the aluminum cap and flip-off seal of vial may be imprinted with the following statement: ***Call Dr. if the dose is > than 100 mg/m^2/cycle.***

CONTRAINDICATION(S)

CISWEL™ is contraindicated in patients with pre-existing renal impairment. CISWEL™ should not be employed in myelosuppressed patients, or patients with hearing impairment. CISWEL™ is contraindicated in patients with a history of allergic reactions to cisplatin or other platinumcontaining compounds.

ADVERSE REACTION(S)

Reports of various side effects of cisplatin, has limited the use

Nephrotoxicity (kidney damage) is a major concern with cisplatin therapy. The dose is reduced when the patient's creatinine clearance is low. Adequate hydration and diuresis is thus required to prevent renal damage. The nephrotoxicity of platinum class of drugs seems to be related to reactive oxygen species and in animal models can be ameliorated by free radical scavenging agents (e.g., amifostine). This is a dose limiting toxicity. Dose related and cumulative renal insufficiency is one of the major dose limiting toxicity of cisplatin. Reports suggest renal toxicity in 28-36 % of patients treated with a single dose of 50 mg/m^2, noted during the second week after the dose and is manifested by elevations in BUN, creatinine, serum uric acid and/or a decrease in creatinine clearance. **Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.** Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using 6-8 hour infusion with intravenous hydration and mannitol has been used to reduce nephrotoxicity. However renal toxicity still can occur after utilization of these procedures.

Neurotoxicity (nerve damage) can be predicted by performing nerve conduction studies before and after treatment. Neurotoxicity is usually characterized by peripheral neuropathy. Neuropathies usually occur after prolonged therapy (4-7 months); however neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin although rare. Cisplatin therapy should be discontinued when symptoms are first observed. Neuropathy however may progress further even after stopping treatment. Reports on preliminary evidence suggest that peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy. Lhermitte's sign, dorsal column myelopathy and autonomic neuropathy are also reported. Loss of taste and seizures may accompany muscle cramps defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration in patients with a relatively advanced symptomatic stage of peripheral neuropathy receiving a relatively high cumulative dose of cisplatin.

Cisplatin is one of the most emetogenic chemotherapy agents, but this is often managed with prophylactic anti-emetics (ondansetron, granisetron, etc.) in combination with corticosteroids. Aprepitant combined with ondansetron and dexamethasone has been shown to be better for highly emetogenic chemotherapy than just ondansetron and dexamethasone.

Ototoxicity (hearing loss) is one of the unavoidable side effects of cisplatin therapy and unfortunately there is at present no effective treatment to prevent this side effect, which may be severe. Audiometric analysis may be necessary to assess the severity of ototoxicity prior to initiation of therapy and prior to subsequent doses of cisplatin. Other drugs (such as the aminoglycoside antibiotic class) may also cause ototoxicity and the administration of this class of antibiotics in patients receiving cisplatin should be strictly avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species. Ototoxicity is manifested by tinnitus and/or hearing loss in the high frequency range (4,000-8,000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Deafness after the initial dose of cisplatin has been reported rarely. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation. It is unclear whether cisplatin induced ototoxicity is reversible. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Vestibular toxicity has also been reported. Ototoxicity may become more severe in patients being treated with other drugs with nephrotoxic potential.

Electrolyte disturbances may be seen in patients on cisplatin therapy; these primarily include hypomagnesaemia, hypokalaemia and hypocalcaemia. Hypocalcaemia occurs in those with low serum magnesium secondary to cisplatin hence it may not primarily be due to cisplatin. Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has occasionally been reported in those patients with hypocalcemia and hypomagnesemia. Generally normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin. Inappropriate antidiuretic hormone syndrome has also been reported.

Reports suggest that myelosuppression occurs in 25-30 % of patients treated with cisplatin and the nadirs in circulating platelets, leukocytes occur between days 18-23 (range 7.5-45) with most patients recovering by day 39 (range 13-62). Leukopenia and thrombocytopenia are often more pronounced at higher doses (> 50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 ml) is reported to occur at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infections have also been reported in patients with neutropenia. Elderly patients may be more susceptible to myelosuppression. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has also been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of cisplatin has rarely been reported in humans.

Marked nausea and vomiting occur in almost all patients treated with cisplatin and as with other platinum agents are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within 1-4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has been reported to occur in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea may also be seen in patients on cisplatin therapy.

Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents may be rare; often events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed for vascular complications. Raynaud's phenomenon may also occur in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added although not essential factor associated with this event. However it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3-5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.