
DBL™ CISPLATIN INJECTION

Cisplatin

Description

DBL™ Cisplatin Injection is a sterile solution of Cisplatin 1 mg/mL, Mannitol BP 1 mg/mL and Sodium Chloride BP 9 mg/mL in Water for Injections BP. The solution does not contain any preservative.

Pharmacology

Cisplatin is an antineoplastic agent with biochemical properties similar to those of bifunctional alkylating agents. The drug inhibits DNA synthesis by producing intrastrand and interstrand crosslinks in DNA. Protein and RNA synthesis are also inhibited to a lesser extent. Cisplatin does not appear to be cell-cycle specific.

Pharmacokinetics

There is good uptake of cisplatin by the kidneys, liver and intestine. More than 90% of platinum containing species remaining in the blood are bound (possibly irreversibly) to plasma proteins.

The clearance of total platinum from plasma is rapid during the first four hours after intravenous administration, but then proceeds more slowly because of covalent binding to serum proteins. Levels of unbound platinum fall with a half-life of 20 minutes to 1 hour depending on the rate of drug infusion. The elimination of intact drug and various platinum-containing biotransformation products is via the urine. About 15 - 25% of administered platinum is rapidly excreted in the first 2 - 4 hours after administration of cisplatin. This early excretion is mostly of intact cisplatin. In the first 24 hours after administration, 20 - 80% is excreted, the remainder representing drug bound to tissues or plasma protein.

Indications

DBL™ Cisplatin Injection is indicated for the palliative treatment of metastatic non-seminomatous germ cell carcinoma, advanced-stage refractory ovarian carcinoma, advanced-stage refractory bladder carcinoma and refractory squamous cell carcinoma of the head and neck. It may be used as a single agent or in combination with other chemotherapeutic agents. It may be employed, in appropriate circumstances, in addition to other modalities, eg radiotherapy or surgery.

Contraindications

Use of cisplatin is contraindicated in patients with a history of hypersensitivity to cisplatin or other platinum-containing compounds, in pregnancy or lactation and in patients with renal impairment. Cisplatin should not be used in patients with hearing impairment or myelosuppression.

Use in pregnancy (Category D)

Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. Cisplatin may be toxic to the foetal urogenital tract. Patients should be advised to avoid becoming pregnant.

Use in lactation

It is not known whether cisplatin is excreted in breast milk. To avoid possible harmful effects in the infant, breastfeeding is not advised during cisplatin therapy.

Precautions

Only individuals experienced in antineoplastic therapy should use cisplatin.

Renal function

Measurements of BUN, serum creatinine and creatinine clearance should be taken before initiating cisplatin therapy, and prior to subsequent doses, as toxicity is cumulative. Cisplatin is recommended to be given once every 3 - 4 weeks. Hydration is recommended to minimise nephrotoxicity.

Cumulative and dose-related renal insufficiency is the major dose-limiting toxicity of cisplatin. The most commonly observed change in renal function has been a fall in glomerular filtration rate reflected by a rise in serum creatinine. Renal function must return to acceptable limits (serum creatinine below 0.14 mmol/L and/or blood urea below 9 mmol/L) before further doses are given.

Ototoxicity

Tinnitus or occasional decreased ability to hear normal conversation are indications of ototoxicity, which have been frequently observed. Abnormalities of audiometric testing are more common and hearing loss can be unilateral or bilateral; frequency and severity increase with repeated doses, and may not be reversible, but mostly occur in the 4,000 - 8,000 Hz range.

As ototoxicity of cisplatin is cumulative, audiometric testing should be performed, if possible prior to initiation of therapy and at regular intervals thereafter, particularly if the clinical symptoms of tinnitus or hearing impairment occur. Radiotherapy may enhance ototoxicity.

Myelosuppression

This may occur in patients treated with cisplatin. The nadirs in circulating platelets and leucocytes generally occur between days 18 - 32 (range 7.3 - 45) with most patients recovering by day 39 (range 13 - 62). Leucopenia and thrombocytopenia are more pronounced at doses greater than 50 mg/m². Anaemia (decrease of greater than 2 g% haemoglobin) occurs at approximately the same frequency but generally with a later onset than leucopenia and thrombocytopenia.

Subsequent courses of cisplatin should not be instituted until platelets are present at levels greater than 100,000/mm³ and white cells greater than 4,000/mm³. A high incidence of severe anaemia requiring transfusion of packed red cells has been observed in patients receiving combination chemotherapy including cisplatin. Rarely, the drug has caused haemolytic anaemia; direct Coombs - positive results have been reported in a few of these cases.

Peripheral blood counts should be performed at regular intervals for the duration of cisplatin treatment.

Anaphylaxis

Reactions, possibly secondary to cisplatin therapy, have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are at particular risk are those with a prior history or family history of atopy. Facial oedema, wheezing, tachycardia, hypotension and skin rashes of urticarial non-specific maculopapular type can occur within a few minutes of administration. Serious reactions seem to be controlled by IV adrenaline, corticosteroids or antihistamines.

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.

Hypomagnesaemia and hypocalcaemia

Hypomagnesaemia occurs quite frequently with cisplatin administration, while hypocalcaemia occurs less frequently. The loss of magnesium seems to be associated with renal tubular damage which prevents resorption of this cation. Where both electrolytes are deficient, tetany may result. It does not appear to be dose related. Monitoring of electrolytes is necessary.

Neurotoxicity and seizures

Peripheral neuropathy, postural hypotension and seizures may occur with cisplatin administration. This appears to be more common after prolonged administration. The development of clinically significant symptoms should generally contraindicate further cisplatin usage.

Others

Liver function should be monitored periodically. Neurological examinations should also be performed regularly.

As patients undergoing treatment with cisplatin are at an increased risk of bleeding, bruising and infection, it is recommended that extreme care be used when performing necessary invasive procedures.

Alcohol and aspirin should be avoided because of the risk of gastrointestinal bleeding.

Extreme caution should be used where patients have recently been exposed to infections, particularly chicken pox and herpes zoster. Live virus vaccines should not be used in patients undergoing cisplatin therapy.

Dental

The bone marrow depressant effects of cisplatin may result in an increased incidence of microbial infection, delayed healing and gingival bleeding. Dental work should be avoided during cisplatin therapy.

Interactions with other drugs

Potentially nephrotoxic or ototoxic drugs, eg aminoglycoside antibiotics and loop diuretics, may potentiate the nephrotoxic and ototoxic effects of cisplatin.

Incompatibilities

Cisplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come in contact with cisplatin should not be used for preparation or administration of the drug. The stability of cisplatin is adversely affected by the presence of bisulphite, metabisulphite, sodium bicarbonate and fluorouracil.

Adverse Reactions

Cumulative and dose-related renal impairment is the major limiting toxicity of cisplatin. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Regimes of IV hydration, mannitol diuresis and 6-8 hour infusions of cisplatin have been used to reduce the incidence and severity of nephrotoxicity.

Tinnitus and/or high frequency hearing loss has been observed in up to 31% of patients treated with cisplatin. Ototoxicity may be more severe in children and more frequent and severe with repeated doses.

Neurotoxicity, characterised by peripheral neuropathies, both sensory and motor, have occurred in some patients.

Myelosuppression may occur in patients treated with cisplatin. Leucopenia and thrombocytopenia are dose-related and more pronounced at doses greater than 50 mg/m². Leucocyte and platelet nadirs generally occur between days 18 and 23 of treatment, with recovery in most patients by day 39. Anaemia occurs at approximately the same frequency.

Cisplatin induces severe nausea and vomiting in almost all patients. Nausea and vomiting usually begin within 1-4 hours after treatment and may persist for up to a week after treatment.

Hyperuricaemia may occur in patients receiving cisplatin, principally as a result of drug-induced nephrotoxicity. Hyperuricaemia is more pronounced with doses greater than 50 mg/m², with peak levels occurring between 3-5 days after administration of the drug. Allopurinol may be used to reduce serum uric acid levels.

Hypomagnesaemia and hypocalcaemia may develop during cisplatin therapy or following discontinuance of the drug. Hypomagnesaemia and/or hypocalcaemia may be manifested by muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany. Regular monitoring of serum electrolyte levels and replacement where necessary are advisable.

Anaphylactic-like reactions, consisting principally of facial oedema, wheezing, tachycardia and hypotension have been reported in patients previously exposed to cisplatin. The reactions may be controlled by IV adrenaline, corticosteroids and/or antihistamines.

Other adverse reactions to cisplatin which have been reported infrequently include cardiac abnormalities, elevated SGOT and liver damage. Secondary malignancies and acute leukaemia have been known to develop. Extravasation may result from infusion of solutions greater than 0.5 mg/mL cisplatin.

Dosage and Administration

The usual dose in adults and children when used as single agent therapy is 50-100 mg/m² as a single IV infusion every 3-4 weeks, or 15-20 mg/m² as a daily IV infusion for 5 days every 3-4 weeks.

Combination Therapy: Cisplatin is commonly used in combination therapy with the following cytotoxic agents:

1. For the treatment of testicular cancer: vinblastine, bleomycin, actinomycin D.
2. For treatment of ovarian cancer: cyclophosphamide, doxorubicin, (adriamycin), hexamethylmelamine, 5-fluorouracil.
3. For treatment of head and neck cancer: bleomycin, methotrexate.

Subsequent Treatment with Cisplatin: A repeat course of cisplatin should not be given until:

1. The serum creatinine is below 140 micromol/L and/or the plasma urea is below 9mmol/L, and
2. Circulating blood elements are at an acceptable level (platelets at least 100,000/mm³, WBC at least 4000/mm³).

A base line audiogram should be taken and the patient monitored periodically for auditory deterioration.

With impaired liver function

Human studies show a high uptake of cisplatin in the liver. An elevated SGOT has been reported in some cases and the adult dosage should be used with caution.

With impaired renal function

Cisplatin displays high tissue uptake in the kidneys, exhibits dose related and cumulative nephrotoxicity, and is excreted mainly in the urine. In addition, the plasma elimination half-life of cisplatin is prolonged in renal failure.

Caution should be exercised in patients with pre-existing renal dysfunction. Cisplatin is contraindicated in patients with serum creatinine levels greater than 0.2 mmol/L. Repeat courses are not advised until serum creatinine is below 0.14 mmol/L and/or blood urea below 9 mmol/L.

- a. **Pretreatment hydration:** Patients should be adequately hydrated before and for 24 hours after administration of cisplatin to ensure good urinary output and minimise nephrotoxicity. Hydration may be achieved by IV infusion of 2 litres of either sodium chloride IV infusion 0.9% or glucose-saline (eg glucose 4% in one-fifth sodium chloride IV infusion 0.9%) over a 2 hour period. During the last 30 minutes of the pretreatment hydration or after the hydration, 375 mL of 10% mannitol injection may be administered via a side-arm drip.
- b. **Preparation of Cisplatin infusion:** DBL™ Cisplatin Injection should be added to 1 litre of sodium chloride IV infusion 0.9%.
- c. **Treatment:** Following prehydration, administer the cisplatin infusion over 1-2 hours. It has been proposed that a longer infusion time of 6-8 hours may decrease gastrointestinal and renal toxicities.
The IV flask should be covered to preclude light.
- d. **Post-treatment hydration:** Adequate hydration and urinary output must be maintained during the 24 hours following infusion. It has been suggested that IV hydration continue after treatment with the aim to administer 2 litres of sodium chloride IV infusion 0.9% or glucose-saline over a period of 6-12 hours.

Overdosage

In the event of overdosage or toxic reactions, symptomatic or supportive measures should be taken. Patients should be monitored for 3 to 4 weeks in case of delayed toxicity.

Storage

Store between 15°C – 25°C. (Do not refrigerate. Do not freeze). Protect from light.

Stability

Cisplatin 0.15 mg/mL in sodium chloride IV infusion 0.9% is chemically stable for 24 hours when stored at room temperature and protected from light. The solution does not contain any antimicrobial preservatives and to avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation. Infusion should be completed within 24 hours of preparation and any residue discarded.

Medicine Classification

Prescription Medicine

Presentation

<u>Strength</u>	<u>Pack Size</u>
10 mg/10 mL	1x 10 mL vial
50 mg/50 mL	1 x 50 mL vial
100 mg/100 mL	1 x 100 mL vial

Name and Address

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