Carplatin Injection

Carboplatin BP Injection

PRESENTATION : Carplatin150 Injection: Each vial contains 15 ml solution of Carboplatin BP 150 mg (10 mg/ ml).

Carplatin 450 Injection: Each vial contains 45 ml solution of Carboplatin BP 450 mg (10 mg/ ml).

Mechanism of Action: Carboplatin is an alkylating agent which covalently binds to DNA; possible cross-linking and interference with the function of DNA.

Pharmacokinetics:

Distribution: Volume of distribution: 16 L/kg; Into liver, kidney, skin, and tumor tissue.

Protein binding: 0%; platinum is 30% irreversibly bound.

Half-life elimination: Terminal: 22-40 hours; Clcr >60 mUminute: 2.5-5.9 hours.

Excretion: Urine (~60% to 90%) within 24 hours.

INDICATIONS : Carboplatin Injection is indicated for the initial treatment of advanced ovarian carcinoma of epithelial origin in established combination with other approved chemotherapeutic agents. It is also indicated for the palliative treatment of patient with ovarian carcinoma recurrent after prior chemo therapy.

DOSAGE AND ADMINISTRATION :

Notes Needles or intravenous sets containing aluminum parts that may come in contact with Carplatin injection should not be used for the preparation or administration. Aluminum reacts with Carplatin causing precipitate formation and/or loss of potency. Procedures for proper handling and disposal of anti-cancer drugs should be implemented. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Dosage

After dilution, Carplatin should be used by the intravenous route only. The recommended dosage of Carplatin in previously untreated adult patients with normal kidney function is 400 mg/m^2 as a single I.V. dose administered by a 15 to 60 minute infusion. Therapy should not be repeated until four weeks after the previous Carplatin course and/or until the neutrophil count is at least 2000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Reduction of the initial dosage by 20-25% (i.e, 300-320 mg/m^2) is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG-Zubrod 2-4 or Karnofsky below 80). For patients age 65 and over, dosage adjustment, initially or subsequently, may be necessary, dependent on the physical condition of the patient.

Determination of the hematologic nadir by weekly blood count during the initial courses of treatment with Carplatin is recommended for dosage adjustment for subsequent courses of therapy.

Impaired renal function

The optional use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematologic nadirs and renal function. Patients with creatinine clearance values below 60mL/min are at increased risk of severe myelosuppression. The frequency of severe leukopenia, neutropenia, or thrombocytopenia has been maintained at about 25% with the following dosage recommendations:

Baseline Creatinine Clearance	Initial Dose (Day 1)
41-59 mL/min	250mg/m^2 IV
16-40 mL/min	200mg/m^2 IV

Insufficient data exist on the use of Carboplatin in patients with creatinine clearance of 15 mL/min or less to permit a recommendation for treatment. All of the above dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance and to the acceptable level of myelosuppression.

Combination Therapy

The optimal use of Carplatin in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted.

Dilution for IV Infusion: Vials of Carboplatin may be further diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection, to concentrations as low as 0.5 mg/mL. Diluted solutions are stable for 8 hours at room temperature (25°C), in light and dark storage conditions. Discard unused portion 8 hours after dilution. Dilutions prepared as directed with 5% Dextrose Injection or 0.9% Sodium Chloride Injection are stable for 48 hours under refrigerator from the time of initial reconstitution, after which time the unused portion should be discarded.

CONTRAINDICATIONS : Carplatin is contraindicated in patients with pre-existing severe renal impairment, unless in the judgement of the physician and patient, the possible benefits of treatment outweigh the risks. Carboplatin should not be employed in severely myelosuppressed patients. Carboplatin is also contraindicated in patients with a history of severe allergic reactions to Carboplatin, other platinum containing compounds, or mannitol. Carboplatin is contraindicated in patients with bleeding tumours.

PRECAUTIONS : Carplatin 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. Peripheral blood counts and renal and hepatic function tests should be monitored closely. Blood counts at the beginning of the therapy and weekly to assess haematologic nadir for subsequent dose adjustment are recommended. Neurologic evaluations should also be performed on a regular basis. The drug should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen. Carboplatin myelosuppression is closely related to its renal clearance; patients with abnormal kidney function or receiving concomitant therapy with other drugs with nephrotoxic potential are likely to experience more severe and prolonged myelotoxicity. Renal function parameters should therefore be carefully assessed before and during therapy. Carboplatin courses should not be repeated more frequently than monthly under normal circumstances. Thrombocytopenia, leucopenia and anaemia which are dose dependant and dose-limiting occur after administration of Carboplatin. Frequent monitoring of peripheral blood counts is recommended throughout and following the therapy with Carboplatin.

Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully with respect to dosages and timing in order to minimize addictive effects. Supportive transfusional therapy might be required in patients who suffer severe myelosuppression. Anemia is frequent and cumulative. Transfusional support is often needed during treatment with Carboplatin, particularly in patients receiving prolonged therapy. Carboplatin can cause nausea and vomiting. Premedication with antiemetics and prolongation of time of Carboplatin administration by continuous infusion or over five consecutive days have been reported to be useful in reducing the incidence and intensity of these effects. Renal function impairment may be encountered with Carboplatin. Although no clinical evidenceon compounding nephrotoxicity has been accumulated, it is recommended not to combine Carboplatin with aminoglycosides or other nephrotoxic compounds. As for other platinum coordination compounds, allergic reactions to Carboplatin have been reported. These may occur within five minutes of administration and should be managed with appropriate supportive therapy.

OVERDOSE : There is no known antidote for Carboplatin overdosage. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal function. Use of higher than recommended doses of Carboplatin has been associated with loss of vision.

ADVERSE EFFECTS : Incidences of adverse reactions reported here under are based on cumulative data obtained in a large group of patients with various pretreatment prognastic features.

Haematologic toxicity Bone marrow suppression is the dose-limited toxicity of Carboplatin. At maximum tolerated dosages of Carboplatin administered as a single agent, thrombocytopenia, with platelet counts of less than 50,000/mm^3, occurs in 25% of the patients. The nadir usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy. Neutropenia with granulocyte counts below 1,000/mm^3 occurs in 18% of patients. Leucopenia, with nadir WBC counts of less than 2000/mm^3, occurs in 14% of the patients but its recovery from the day of nadir (day 14-28) may be slower and usually occurs within 42 days from the start of therapy. Anaemia with haemoglobin values below 11 g/dL has been is observed in 71% of the patients. Myelosuppression may be more severe and prolonged in patients with impaired kidney function, extensive prior treatment, poor performance status and age above 65. Myelosuppression is also worsened by therapy combining Carboplatin with other compounds that are toxic to the bone marrow. Myelosuppression is usually reversive and not cumulative when Carboplatin is used as a single agent and at the recommended dosages and frequencies of administration. Infectious and haemorrhagic complications have been reported in 4% and 5% of the patients given Carboplatin, respectively.

Nephrotoxicity When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that Carboplatin has been administered without high-volume fluid hydration and/or forced diuresis. Elevation of serum creatinine occurs in 6% of patients, elevation of blood urea nitrogen in 14%, and of uric acid in 5% of patients. These are usually mild and are reversible in about one-half the patients. Creatinine clearance has proven. to be the most sensitive renal function measure in patients receiving Carboplatin. Twenty-seven percent of patients who have a baseline value of 60 mL/min or greater, experience a reduction in creatinine clearance during Carboplatin therapy. Decreases in serum electrolytes sodium, potassium, calcium, magnesium occur in 29%, 20%, 22%, 29% of patients respectively. Spontaneous reports of early hypotension have been reported which were generally reversed by sodium replacements or free water restriction.

Gastrointestinal toxicity Nausea without vomiting occurs in about 15% of the patients receiving Carboplatin; vomiting has been reported in 65% of the patients. One-third of those patients who vomit suffer severe emesis. Nausea and vomiting usually disappear within 24 hours after treatment and are usually responsive to (and may be prevented by) antiemetic medication. Other gastrointestinal side effects consist of pain (17%); diarrhoea (6%), and constipation (6%). Anorexia has been reported from post-marketing surveillance.

Allergic reactions Infrequent reactions to Carboplatin have been reported in less than 2% of the patients. These reactions are similar to those observed after administration of other platinum-containing compounds, i.e. erythematous rash, fever with no other apparent cause, pruritus, urticaria, rarely bronchospasm and hypotension.

Hepatic Toxicity The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

Neurotoxicity The incidence of peripheral neuropathies after treatment with Carboplatin is 4%. In the majority of the patients neurotoxicity is limited to paresthesias and decreased deep tendon reflexes. The frequency and intensity of this side effect increase in patients previously treated with cisplatin. Paresthesias present before commencing Carboplatin therapy, particularly if related prior cisplatin treatment, may persist or worsen during treatment with Carboplatin. Central nervous symptoms have been reported in 5% of patients and often appear to be related to the use of antiemectics. The overall frequency of neurologic side effects seems to be increased in patients receiving Carboplatin in combination. This may also be related to longer cumulative exposure.

Incompatibilities Contact with Aluminium - containing injection and infusion materials should be avoided.

Use in Pregnancy and Lactation : Pregnancy Category D. There are no adequate and well controlled studies in pregnant women. Carplatin has been reported to be found in human milk. It is not known whether Carboplatin is excreted in human.

DRUG INTERACTIONS : This product should not be mixed with other drugs. The renal effects of neurotoxic compounds may be potentiated by Carboplatin.

Increased toxicity: Nephrotoxic drugs; Aminoglycosides increase risk of ototoxicity.

Docetaxel, Paclitaxel (taxane derivatives): When administered as sequential infusions, taxane derivatives should be administered before Platinum derivatives to limit myelosuppression and to enhance efficacy.

Storage :

Store below 25° C in a dry place, Do not Refrigerate. Keep all medicines out of reach of children.

Presentation and Packaging

Carplatin 150 Injection: Each box contains 1 vial of 15 ml solution.

Carplatin 450 Injection: Each box contains 1 vial of 45 ml solution.

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