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IND

Oxaliplatin

50 mg/10 ml **100 mg/20 ml**

(5 mg/ml)

Injection USP

SOXPLAT™ 50/100

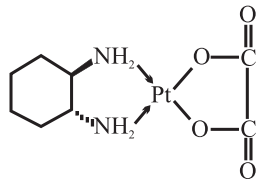
DESCRIPTION

Oxaliplatin a cell cycle-phase nonspecific antineoplastic drug belongs to a new class of platinum agent that contains a platinum atom complexed with oxalate and diaminocyclohexane (DACH).

COMPOSITION

Each ml contains:
Oxaliplatin USP 5mg

CHEMICAL STRUCTURE



Chemically Oxaliplatin is trans-l-diaminocyclohexane oxalatoplatinum or cis-[oxalato (trans-l- 1, 2-diaminocyclohexane) platinum (II)]. The empirical formula of Oxaliplatin is $C_8H_{14}N_2O_4Pt$. The molecular weight of Oxaliplatin is 397.30. Oxaliplatin is slightly soluble in water and methanol, and insoluble in ethanol.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The exact mechanism of action of oxaliplatin is not known. The mechanism of action of oxaliplatin is probably similar to that of cisplatin. Oxaliplatin forms reactive platinum complexes that are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Oxaliplatin is not cross resistant to cisplatin or carboplatin, probably due to the DACH group and resistance to DNA mismatch repair. Oxaliplatin is a radiation sensitizing agent.

PHARMACOKINETICS

After Intravenous distribution, Oxaliplatin is mainly accumulated in erythrocytes and does not diffuse into the plasma. 85-88% of platinum is protein bound in the first 5 hours after administration; Oxaliplatin undergoes rapid nonenzymatic biotransformation to reactive platinum complexes. The active metabolites of oxaliplatin are DACH platinum species. Oxaliplatin is excreted mainly by renal excretion. Approximately 50% of the administered dose is excreted in the urine with in the first 3 days. Fecal excretion is approximately 0.5% per day and reaches 5%of the total dose by day 11. The terminal half-life of ultrafilterable platinum (oxaliplatin and free oxaliplatin metabolites) is 273±19 hrs. The platinum-elimination from the erythrocytes takes about 48 days.

DRUG INTERACTIONS

Oxaliplatin induces irinotecan-related cholinergic syndrome by potentiating irinotecan inhibition of acetylcholinesterase.
Oxaliplatin has no influence on fluorouracil and topotecan pharmacokinetics. Preclinical studies have shown oxaliplatin to be synergistic with fluorouracil and SN-38, the active metabolite of irinotecan.
There are no other studies documenting any major interactions of oxaliplatin with other drugs.

CLINICAL STUDIES

Oxaliplatin as a first line, single-agent therapy metastatic colorectal cancer achieved an overall response rate of 24.3% in a phase II trial of 36 assessable chemotherapy naive patients. The dose was 130 mg/m^2 as a 2-hour infusion on days 1 and 21, for a median of 5.5 cycles (median cumulative dose, 670 mg/m^2). Overall median survival duration was 395 days with about 74% of patients alive at 12 months.

The addition of oxaliplatin to adjuvant therapy with leucovorin and fluorouracil for advanced colorectal cancer (n = 420) resulted in significantly longer progression-free survival (9.0 versus 6.2months: p=0.0001) and better response rate (50% versus 21.9%; p=0.0001); overall survival also increased, but not significantly (16.2 versus 14.7 months: p=0.12). Patients with adenocarcinoma of the colon or rectum with unresectable metastases were included; any previous adjuvant chemotherapy must have been completed atleast 6 months prior to study entrance. In both arms of the study, a 2-hour infusion of leucovorin (200mg/m^2/day) followed by fluorouracil (bolus of 400mg/m^2/day and 22 hour infusion of 600mg/m^2/day) was administered for 2 consecutive days every 2 weeks. In the oxaliplatin arm, a 2-hour infusion of oxaliplatin (85mg/m^2 on day 1 only) was administered concurrently with leucovorin; antiemetic prophylaxis was administered only to patients in the oxaliplatin arm. Toxicity was more common in patients receiving oxaliplatin and included Grade 3/4 neutropenia (41.7% versus 5.3%; p less than 0.001), grade 3 neurotoxicity (18.2% versus 0.0%; p less than 0.001), grade 3/4 diarrhea (11.9% versus 5.3%; p=0.015), and grade 3/4 mucositis (5.8% versus 1.5%; p=0.019).

INDICATIONS

Oxaliplatin is indicated in the treatment of metastatic colorectal cancers after failure of treatment with fluoropyrimidines, alone by monochemotherapy or along with fluoropyrimidines.

CONTRAINDICATIONS

Oxaliplatin is contraindicated in patients with:

- History of severe allergy to the drug
- Severe pre-existing peripheral neuropathy
- Severe renal dysfunction (Crcl<30ml/min)
- Pregnancy and breast feeding

ADVERSE REACTIONS

Commonly occurring adverse effects of Oxaliplatin are:

- Sensory neuropathy (dose limiting toxicity)
- Anaemia
- Fever
- Nausea& vomiting
- Liver function abnormalities
- Infections
- Alopecia
- Pharyngolaryngeal dysesthesia

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Other side effects that become more pronounced when used in combination with fluorouracil and leucovorin are:

- Neutropenia
- Thrombocytopenia
- Diarrhoea
- Mucositis

WARNING AND PRECAUTIONS

- Oxaliplatin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents
- Aluminum has been reported to cause degradation of platinum compounds and hence needles or intravenous administration sets containing aluminium parts that may come in contact with oxaliplatin should not be used for the preparation or mixing of the drug.
- Oxaliplatin should not be administered undiluted. Dilute with 5% Dextrose infusion
- Oxaliplatin should not be mixed with any other medication and should not be administered simultaneously by the same infusion line.
- Caution is recommended while administering oxaliplatin to patients with known hypersensitivity to other platinum agents.
- Oxaliplatin is incompatible in solution with alkaline medication or media and hence it is advised that oxaliplatin should never be diluted with Sodium Chloride/Chloride-containing infusion solutions.
- Oxaliplatin has been found to be mutagenic in mammalian in vitro mutation chromosome test. Although carcinogenic studies have not been done, Oxaliplatin is considered a probable carcinogen.
- Oxaliplatin is embryotoxic and fetotoxic in rats. Oxaliplatin may cause fetal harm when administered to pregnant women; the patient should be apprised of the potential hazard to the fetus and potential risk for loss at the pregnancy if there is exposure to oxaliplatin during pregnancy.
- It is not known whether oxaliplatin is excreted in human milk or not. Caution should be exercised when oxaliplatin is administered to a nursing woman as many drugs are excreted in human milk.
- Inspect the solution visually for particulate matter and discolouration prior to administration.

DOSAGE AND ADMINISTRATION

The recommended dose of oxaliplatin injection for single agent studies is 130 mg/m^2 given intravenously over at least 2 hours, every three-four weeks. In combination studies with 5-FU, with or without folinic acid, the recommended dose of oxaliplatin is 130 mg/m^2 every 3 weeks and 85 mg/m^2 every two weeks.

To be diluted and given as slow I.V. infusion. The preparation for infusion can be stored for 24 hours at room temperature.

DOSE MODIFICATIONS

As peripheral neuropathy is the dose limiting toxicity, following dose adjustments have to be made when it occurs:

- If symptoms last longer than 7 days and are troublesome, the subsequent dose of oxaliplatin should be reduced by 25%
- If paraesthesia persists until the next cycle, the subsequent dose of oxaliplatin should be reduced by 25%
- Oxaliplatin should be discontinued if troublesome paraesthesia or functional impairment persists until the next cycle
- Resumption of therapy should be considered if these symptoms improve following discontinuation of oxaliplatin therapy

When oxaliplatin is combined with fluorouracil, the usual dose adjustments for 5-fluorouracil associated toxicities should apply. In addition the dose of oxaliplatin should be reduced by 25% if grade 3-4 diarrhoea, neutropenia, thrombocytopenia occur.

OVERDOSAGE

There is no known antidote for oxaliplatin overdosage: In general, supportive care and frequent monitoring at vital signs should be administered.

STORAGE

Store at 25° C excursions permitted to 15° to 30°C. Do not freeze. Protect from light.

PRESENTATION

Soxplat is available as 10 ml and 20 ml fill containing 50 mg and 100 mg of oxaliplatin, respectively.

REFERENCES

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