Oxaliplatin: Third-Generation Platinum Analog

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Drug name: Oxaliplatin also is known as Eloxatin™, which is distributed by Sanofi-Synthelabo, Inc. (New York, NY), and manufactured for Sanofi-Synthelabo, Inc., by Ben Venue Laboratories (Bedford, OH).

Classification: Oxaliplatin is categorized as a third-generation platinum analog, without renal toxicity.

Action: Oxaliplatin is cell-cycle nonspecific and causes inter- and intra-cross linking of DNA strands, thus preventing DNA replication and transcription and causing cell death.

Indications: Oxaliplatin is U.S. Food and Drug Administration (FDA) approved in combination with infusional 5-fluorouracil (5-FU) and leucovorin for second-line treatment of patients with metastatic colorectal cancer that has recurred or progressed during or within six months of completing first-line chemotherapy with 5-FU, leucovorin, and irinotecan.

Metabolism: After IV administration, oxaliplatin is converted to several derivatives via displacement of an oxalate ligand. The exact mechanism is unknown. Following a two-hour drug infusion, 15% of the drug is found in the systemic circulation, with the remaining 85% found in tissue or excreted in the urine. Ninety percent of platinum is bound irreversibly to plasma proteins, chiefly albumin and gamma globulins. In addition, oxaliplatin is known to bind irreversibly in red blood cells, where it appears to have no clinical activity. The drug does not accumulate between two-week doses of oxaliplatin.

Excretion: The majority of oxaliplatin is eliminated by the kidneys. Five days after a two-hour infusion of oxaliplatin, 54% of the drug was found in the urine and 2% was excreted in feces. Drug clearance from plasma is swift, and renal clearance correlates with the glomerular filtration rate. Thus, the area under the curve (AUC) or active drug in the serum increases as renal function decreases: At mild dysfunction (creatinine clearance of 50–80 mL/minute), AUC increased 60%; at moderate dysfunction (30–50 mL/minute), AUC increased 140%; and at severe renal dysfunction (< 30 ml/minute), AUC increased 190%. Although patients with compromised renal function were not studied, appropriate dose reduction should be considered in these patients. No differences existed between men and women with normal renal function.

Half-life: Oxaliplatin has a triphasic fall in serum drug levels. Initially, the drug has two short half-life distribution phases, $t_{½\alpha}$ 0.43 hours and $t_{½\beta}$ 16.8 hours, followed by a terminal half-life of $t_{½\gamma}$ 391 hours.

Effect on blood counts: Oxaliplatin causes myelosuppression, the risk of which is increased when given in combination with infusional 5-FU together with leucovorin. The incidence of the combination is neutropenia 73% (44% grades 3 or 4, 6% febrile neutropenia), thrombocytopenia 64% (4% grades 3 or 4), and anemia 81% (2% grades 3 or 4). Absolute neutrophil count (ANC) nadir occurs from days 7–10.

Adverse reactions and events: Neuropathy is the dose-limiting toxicity, which can be broken down into acute and chronic persistent neurotoxicity.

- Acute sensory neuropathy may affect up to 56% of patients, is temporary and reversible, and occurs during, within hours, or up to 14 days of oxaliplatin administration. It often is precipitated by exposure to cold and characterized by dysesthesias, transient paresthesias, or hypothesias of the hands, feet, perioral area, and throat. Acute events can be minimized by slower infusion of oxaliplatin, increasing the infusion time from two to six hours, as this lowers peak serum levels.
- Pharyngolaryngeal dysesthesia is characterized by a sensation of discomfort or tightness in the back of the throat and the inability to breathe. It may be accompanied by jaw pain and is often very frightening and precipitated by ingestion of a cold beverage or ice. Patients may feel like they are not breathing when, in fact, they are breathing without difficulty—on physical examination, the oxygen saturation assessment is unchanged compared to baseline. Other acute neuromuscular events include jaw spasm, cramping of arms or hands, abnormal tongue sensation, dysarthria (i.e., difficulty articulating words), eye pain, and a feeling of chest pressure.
- Chronic, persistent sensory peripheral neuropathy (PN) lasts longer than 14 days and, in clinical trials, occurred in 48% of patients receiving six cycles of oxaliplatin, leucovorin, and infusional 5-FU. This usually occurs when a cumulative dose of 800 mg/m^2 has been given. Symptoms include paresthesias (feeling of numbness, tingling, or "pins and needles"), dysesthesias (unpleasant sensation of numbness, burning, tingling), hypoesthesias (decreased response to a known stimulation), and proprioception (knowing where body parts are in space) deficits, with resulting difficulty writing, walking, swallowing, and buttoning buttons. If allowed to progress, neuropathy will involve motor pathways with disabling toxicity.
- Other acute side effects of oxaliplatin alone are nausea (64%), diarrhea (46%), vomiting (37%), fever (25%), dyspnea (13%), back pain (11%), coughing (11%), and injection site reactions (9%). Intermediately occurring side effects include fatigue (61%), elevated liver function test (aspartate aminotransferase 54%, amino transaminase 36%, and total bilirubin 13%), ab-

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