DRUG NAME: Oxaliplatin

SYNONYM(S): ACT-078, l-OHP, LOHP, oxalatoplatin, oxaliplatinum

COMMON TRADE NAME(S): ELOXATIN®

CLASSIFICATION: Alkylating agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Oxaliplatin belongs to a new class of platinum agent. It contains a platinum atom complexed with oxalate and diaminocyclohexane (DACH). The bulky DACH is thought to contribute greater cytotoxicity than cisplatin and carboplatin.[1] The exact mechanism of action of oxaliplatin is not known. Oxaliplatin forms reactive platinum complexes which are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Oxaliplatin is not generally cross-resistant to cisplatin or carboplatin, possibly due to the DACH group and resistance to DNA mismatch repair.[1,2] Preclinical studies have shown oxaliplatin to be synergistic with fluorouracil and SN-38, the active metabolite of irinotecan.[3] Oxaliplatin is a radiation-sensitizing agent.[4,5] It is cell cycle phase-nonspecific.[6]

PHARMACOKINETICS:

Interpatient variability	inter- and intra-subject variability is low[6]	
Distribution	minimal in plasma; accumulation in erythrocytes does not diffuse into plasma or act as a drug reservoir	
	cross blood brain barrier?	no information found
	volume of distribution	ultrafilterable platinum*: 582 ± 261 L[6]
	plasma protein binding	70-95%
Metabolism	rapid nonenzymatic biotransformation to reactive platinum complexes[7]	
	active metabolite(s)	DACH platinum species[6]
	inactive metabolite(s)	several conjugates,[6] including the 1,2-DACH-platinum dichloride (2%) associated with neurotoxicity[3]
Excretion	platinum is mainly by renal excretion and tissue distribution,[8] while platinum metabolites are mainly by renal excretion[1]	
	urine	50% within 3 days[9]
	feces	minimal[9]
	terminal half life	ultrafilterable platinum*: 273 ± 19 h[6] platinum elimination from erythrocytes: 48 days[1]
	clearance	ultrafilterable platinum*: 10.1 ± 3.07 L/h[6]

Adapted from reference[1] unless specified otherwise.

∗Ultrafilterable platinum consists of oxaliplatin and free oxaliplatin metabolites.

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USES:

Primary uses:

*Colorectal cancer[10-12]

Other uses:

Breast cancer[13]
Gastric cancer[14]
Germ cell cancer[15]
Head and neck cancer[16]
Lung cancer, non-small cell[17]
Lymphoma, non-Hodgkin's[18]
Mesothelioma[19,20]
Ovarian cancer[21,22]
Pancreatic cancer[23]
Prostate cancer[24]

*Health Canada approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to oxaliplatin or other platinum agents (e.g., cisplatin, carboplatin)[6]
- peripheral sensory neuropathy interfering with function or severe renal dysfunction (CrCl < 30 mL/min)[6]

Caution:

- QT prolongation and torsades de pointes are reported; use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically.[25,26]

Special populations:

- ***elderly patients*** over 65 may be at higher risk of severe (grades 3-4) diarrhea[11]
- ***women*** may be at higher risk of severe (grades 3-4) neutropenia[11]

Carcinogenicity: Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been done.[6]

Mutagenicity: Mutagenic in mammalian *in vitro* mutation chromosome tests.[6]

Fertility: no information found

Pregnancy: Oxaliplatin produced embryo-fetal toxicity in rats.[6]

Breastfeeding is not recommended due to the potential secretion into breast milk.[6]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. ***Incidence of adverse events*** is generally similar when oxaliplatin is used as a single agent or in combination with fluorouracil and leucovorin, although severe (grades 3-4) diarrhea, nausea and vomiting, and neurotoxicity are more common with combination therapy.[1,27]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylaxis (0.5-2%)[6,28,29]
blood/bone marrow febrile neutropenia	anemia (64-83%, severe 4-5%)
	febrile neutropenia (< 2%)
	immune hemolytic anemia (rare)[30]
	neutropenia: single agent (15%, severe 3%); with fluorouracil and leucovorin (66%, severe 38%)
	thrombocytopenia: single agent (41%, severe 3%); with fluorouracil and leucovorin (76%, severe 4%)
constitutional symptoms	fever (36%)
dermatology/skin	alopecia (2%)
general disorders and administration site conditions	*extravasation hazard*: irritant[31-36]; treat as vesicant[37]; see paragraph following **Side Effects** table
	infusion-related (vascular) pain[38] (50-80%); see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* high moderate[39]
	diarrhea: single agent (41%, severe 5%); with fluorouracil and leucovorin (58%, severe 10%)
	mucositis: single agent (4%, severe 2%); with fluorouracil and leucovorin (42%, severe 8%)
	nausea, vomiting (69-71%, severe 12-14%)
hepatic	liver function abnormalities (46%, severe 12%)
infection	infection (23%)
investigations	QT prolongation, torsades de pointes[25,26,40,41]
neurology	central neurotoxicity/reversible posterior leukoencephalopathy syndrome (<1%)[42-46]; see paragraph following **Side Effects** table
	neuropathy, sensory (85-95%); see paragraph following **Side Effects** table
	pharyngolaryngeal dysesthesia (1-2%); see paragraph following **Side Effects** table
renal/genitourinary	renal dysfunction (3%, severe < 1%)
vascular	thromboembolic events, including deep vein thrombosis[47] (1-10%)[47-49]

Adapted from reference[6] unless otherwise specified.

Extravasation of oxaliplatin may sometimes cause severe local inflammation and potentially tissue necrosis.[31-36] The optimal non-pharmacological management of oxaliplatin extravasation is unclear. However, it has been suggested that warm compresses may be preferred over cool compresses[33,50,51] which may theoretically precipitate or worsen peripheral sensory neuropathy. For management of extravasation reactions, see Systemic Therapy Policy Number III-20 Prevention and Management of Extravasation of Chemotherapy.

Infusion-related (vascular) pain is reported to occur in 50-80% of patients treated with oxaliplatin via a peripheral vein. Interventions such as adjusting the oxaliplatin solution pH, diluting or prewarming the infusion solution, and warming the injection site with hot compresses have only had limited effects in reducing vascular pain. Concurrent administration of dextrose 5% with peripheral venous administration of oxaliplatin has been shown to significantly reduce the incidence of vascular pain.[38] Refer to protocol by which patient is being treated.[52]

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Peripheral sensory neuropathy is cumulative, dose-related and usually reversible a few months after stopping treatment. Symptoms include sensory ataxia and dysesthesia of the limbs, mouth, throat and larynx, and may be exacerbated by exposure to cold (e.g., touching cold surface, drinking cold liquid).[1,39] The incidence of grade 2 neuropathy is 10% after 3 treatment cycles and 50% after 10 cycles. Grade 3 neuropathy occurs in 10% after 9 cycles and 50% after 14 cycles, is reversible in 74% of the cases, and begins to recover after 13 weeks. Paresthesia interfering with function (e.g., buttoning clothing, holding objects, writing) is seen in 16% of patients after 4 months of treatment and rarely leads to oxaliplatin withdrawal.[11] Unlike cisplatin, oxaliplatin neuropathy is related to injury to small rather than large sensory fibres.[17] The use of calcium gluconate or magnesium sulfate infusions pre- and/or post oxaliplatin treatment do not appear to reduce or protect against oxaliplatin-induced neurotoxicity.[53-56] Gabapentin PO 100 mg twice daily, with increments of 100 mg PO daily as needed, may be effective in some patients to reduce oxaliplatin neuropathy,[57] while carbamazepine does not appear to be effective.[58] Other agents used with some success include alpha-lipoic acid IV 600 mg weekly for 3-5 weeks, then followed by oral 600 mg three times daily.[59] Oxaliplatin delivered according to 24-hour biologic rhythms (chronomodulated) appears to be associated with less peripheral neuropathy than fixed rate infusion.[1,12]

Pharyngolaryngeal dysesthesia with sporadic reduced sensitivity of the larynx and pharynx is seen in 1-2% of patients shortly after drug infusion. Symptoms usually resolve within hours of onset but the feeling of difficulty in breathing or swallowing may be distressing to the patient. Treatment is usually not needed, although antihistamines and bronchodilators have been used. To prevent recurrence, infusion time should be extended to 6 hours with subsequent treatments.[1,6]

Reversible posterior leukoencephalopathy syndrome (RPLS; also known as PRES) has been associated with oxaliplatin,[42-46] which may cause endothelial dysfunction and lead to vasogenic edema.[43,44] Clinical presentation includes altered mental status, seizures, headache, and loss of vision with associated radiographic abnormality on MRI or CT.[43] Symptom onset may be delayed relative to treatment, with cases reported 8 to 12 days after the first infusion and as long as 6 weeks post treatment.[44,45,60] Management is usually supportive, with control of hypertension, electrolyte replacement, seizure management, and discontinuation of oxaliplatin.[43,44] Although usually reversible, permanent disability and fatalities have been reported.[43,44]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
fluorouracil[61]	no influence on fluorouracil pharmacokinetics		
irinotecan[62-64]	induction of irinotecan-related cholinergic syndrome	may potentiate irinotecan inhibition of acetylcholinesterase	give prophylactic atropine before irinotecan
topotecan[65]	no effects on topotecan pharmacokinetics		
warfarin[66]	significantly higher incidence of INR elevation when administered with oxaliplatin/fluorouracil based regimens	unknown; possible synergy of anticoagulant effect of fluorouracil by oxaliplatin	for oxaliplatin/fluorouracil based regimens only: monitor INR regularly during and for one month following completion of treatment; adjust warfarin dose as needed

Avoid concurrent use of QT/QTc-prolonging drugs if possible. Use caution with drugs that may disrupt electrolyte levels. Correct electrolytes as needed and monitor as applicable.[25]

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SUPPLY AND STORAGE:

Injection:
sanofi-aventis Canada Inc. supplies oxaliplatin as 50 mg and 100 mg single-use vials of sterile lyophilized powder and 50 mg, 100 mg, and 200 mg single-use vials of sterile preservative-free aqueous solution in a concentration of 5 mg/mL. Store at room temperature. Do not freeze. Protect from light for long-term storage.[46]

Sandoz Canada Inc. supplies oxaliplatin as 50 mg, 100 mg, 150 mg, and 200 mg single-use vials of preservative-free aqueous solution in a concentration of 5 mg/mL. Store at room temperature. Do not freeze. Protect from light.[67]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- aluminum-containing IV needles, syringes or sets should not be used to prepare or administer oxaliplatin; aluminum reacts with platinum from oxaliplatin to form a precipitate, resulting in loss of potency[6]
- oxaliplatin should not be combined with leucovorin or leucovorin containing trometamol in the same infusion bag; however, oxaliplatin can be co-administered with leucovorin or leucovorin containing trometamol using a Y-line placed immediately before the site of injection[68,69]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	• duration of administration varies according to protocol: ○ ***in 500 mL D5W over 2 h***[11]***;*** in 250-500 mL D5W over 30 min[9], 3 h[70], or 6 h[12] • administer oxaliplatin before fluoropyrimidines (e.g., fluorouracil)[6] • do not piggyback or flush lines with sodium chloride solution[6]
Continuous infusion	chronomodulated infusion over 5 days using programmable-in-time pump[12]
Intraperitoneal	***hyperthermic intraperitoneal chemotherapy (HIPEC):*** pump solution into abdominal cavity and circulate as per protocol using hyperthermia pump; solutions and dwell time vary by protocol[71-73]
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	investigational, over 4 h[74]
Intravesical	no information found

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or in patients with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	1 week[70]:	35 mg/m² IV for one dose on day 1
	2 weeks[1,10,75]:	85 mg/m² (range 80-100 mg/m²) IV for one dose on day 1
	3 weeks[1,3,75]:	130 mg/m² (range 85-135 mg/m²) IV for one dose on day 1
		30 mg/m²/day by continuous IV infusion for 5 consecutive days (total dose per cycle 150 mg/m²)[76]
		35 mg/m²/day by chronomodulated IV infusion for 5 consecutive days (total dose per cycle 175 mg/m²)[76]
	4 weeks:	85 mg/m² IV for one dose on days 1 and 15 (total dose per cycle 170 mg/m²)[77]
	50 days:	50 mg/m² IV for one dose on days 1,8, 15, 22, 29, and 36 (total dose per cycle 300 mg/m²)[78]
Concurrent radiation:	investigational, 130 mg/m² IV on days 1 and 29 concurrent with radiation[4]	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	

Dosage in neurotoxicity:[6]

Duration of Neurotoxicity	***Severity***	***Dose***
> 7 days[6,11]	troublesome	reduce dose from: 130 mg/m² to 100 mg/m²; or from 85 mg/m² to 65 mg/m²; or from 65 mg/m² to 50 mg/m²
persists until next cycle[6]	no functional impairment	reduce dose from 85 mg/m² to 65 mg/m²
> 7 days[11]	functional impairment	reduce dose from 85 mg/m² to 50 mg/m²
persists until next cycle[6,11]	functional impairment	discontinue*

*if neurotoxicity improves following discontinuation, resumption of therapy may be considered[6,79]

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Dosage in renal failure:

Creatinine clearance (mL/min)	Dose
> 30	100%[80]
< 30	no information found

calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: mild to moderate dysfunction: no adjustment required[6]; severe dysfunction: no information found

Dosage in dialysis: no information found

Children: has been used; effectiveness has not been established[46]

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