DRUG NAME: Topotecan

SYNONYM(S): Topotecan hydrochloride, NSC-609699

COMMON TRADE NAME(S): HYCAMTIN®

CLASSIFICATION: Topoisomerase I inhibitor

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

MECHANISM OF ACTION:

Topotecan is a semisynthetic, water-soluble derivative of camptothecin, which is a cytotoxic alkaloid extracted from plants such as *Camptotheca acuminata*. Topotecan has the same mechanism of action as irinotecan. It inhibits the action of topoisomerase I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication. These single-strand breaks relieve torsional strain and allow DNA replication to proceed. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of the DNA strand, resulting in double strand DNA breakage and cell death.[1] Unlike irinotecan, topotecan is found predominantly in the inactive carboxylate form at neutral pH and it is not a prodrug. As a result, topotecan has different antitumour activities and toxicities from irinotecan.[2] Topotecan is a radiation-sensitizing agent.[3] It is cell cycle phase-specific (S-phase).[4,5]

PHARMACOKINETICS:

Interpatient variability	large interpatient and intrapatient variability[5,6]	
Oral absorption	30-40% absorbed; oral route is being studied in clinical trials.[7,8]	
	time to peak plasma concentration	within 1-2 h[7,8]
Distribution	evenly distributed between blood cells and plasma; extensively distributed into tissues[4]	
	cross blood brain barrier?	CSF to plasma ratio is 29% after a 24-hour infusion and 42% after a 72-hour infusion[4]
	volume of distribution	130 L (reduced by 25% in patients with CrCl of 20-39 mL/min)[1]
	plasma protein binding	35%[1,9]
Metabolism	Undergoes reversible, pH-dependent hydrolysis of the active lactone moiety to the inactive hydroxyacid (carboxylate) form. The lactone form is present at pH $\leq$ 4 and the hydroxyacid form predominates at physiologic pH. Relatively small amount of topotecan is metabolized by hepatic microsomal enzymes to an active metabolite, *N*-demethyltopotecan.[1,4,10] The clinical significance of this metabolite is not known.[4]	
	active metabolite(s)	lactone form, *N*-demethyltopotecan
	inactive metabolite(s)	hydroxyacid form[1], glucuronides of topotecan and *N*-demethyltopotecan[11]
Excretion	biliary and renal excretion	
	bile	extent of biliary excretion not determined[12]
	urine	20-60% of dose
	terminal half life	2-3 h (increased to 5 h in patients with CrCl of 20-40 mL/min)[1]
	clearance	1030 mL/min (decreased by 33% in patients with CrCl of 40-60 mL/min, by 66% with CrCl 20-40 mL/min); (decreased by 33% with bilirubin of 30-255 μmol/L)[1]
Gender	clearance 24% lower in females but no dosage adjustment required[1,9]	
Elderly	no clinically significant difference in females; no information found on males	

Children	clearance similar to adults when given as a 24-hour continuous infusion
Ethnicity	no information found

Adapted from reference[9] unless specified otherwise. Data pertained to 30 min IV infusion unless specified otherwise.

USES:

Primary uses:
*Ovarian cancer[13-15]

Other uses:
*Lung cancer, small cell[16-18]
Gliomas[19]
Leukemia, acute myelogenous[20,21]
Leukemia, chronic myelomonocytic[22,23]
Lung cancer, non-small cell[24]
Multiple myeloma[25]
Myelodysplastic syndrome[22,23,26]
Neuroblastoma[27]
Pancreatic cancer[28,29]
Retinoblastoma[27]
Rhabdomyosarcoma[27,30]
Sarcoma, Ewing's[27]

*Health Canada Therapeutic Products Programme approved indication

SPECIAL PRECAUTIONS:

Renal dysfunction: Contraindicated in patients with severe renal dysfunction (CrCl < 20 mL/min).[9]

Carcinogenicity: There is some evidence linking therapy with topoisomerase I inhibitors such as topotecan to the development of acute leukemias associated with specific chromosomal translocations. Long-term animal studies have not been done.[1]

Mutagenicity: Mutagenic in mammalian *in vitro* and *in vivo* mutation tests, but not mutagenic in bacterial *in vitro* mutation tests.[1,9]

Fertility: No information found.[1]

Pregnancy: FDA Pregnancy Category D.[1] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[1,9]

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.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow febrile neutropenia	***anemia*** (89%, severe 37%); nadir 15 days, recovery within 7 days[1,14]
	leukopenia (97%, severe 85%)[13,14]
	neutropenia (severe 95-97%)[13,14]; nadir 12 days, recovery within 7 days[1,14]
	thrombocytopenia (69%, severe 50%)[13,14]; nadir 15 days, recovery within 5 days[1,14]
	fever or infection with severe neutropenia (25-28%, severe 5%)[13,16]
constitutional symptoms	fatigue (29%, severe 5%)
	fever (28%, severe 1%)[13]
dermatology/skin	*extravasation hazard:* none[4]
	alopecia (49%)
	rash (16%, severe 1%)
gastrointestinal	*emetogenic potential:* low-moderate[13,14]
	anorexia (19%, severe 2%)
	constipation (29%, severe 3%)
	diarrhea (32%, severe 4%)
	nausea (64%, severe 8%)
	stomatitis (18%, severe 1%)
	vomiting (45%, severe 5%)
hepatic	bilirubin elevation (severe <2%)
	hepatic enzymes elevation (8%)
neurology	headache (18%, severe 1%)
	neuropathy-sensory (7%)
pain	abdominal pain (22%, severe 4%)
	arthralgia (6%, severe 1%)[13]
	myalgia (4%)[13]
	pain, includes body pain, back pain and skeletal pain (23%, severe 3%)
pulmonary	cough (15%, severe 1%)
	dyspnea (22%, severe 8%)
secondary malignancy	acute leukemias[1]

Adapted from reference[9] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
docetaxel[31]	administration of docetaxel on day 4 of topotecan therapy decreased docetaxel clearance by 50% and increased docetaxel toxicity	topotecan may alter docetaxel metabolism via CYP3A4 inhibition	administer docetaxel on day 1 of topotecan therapy
phenytoin[10]	increased topotecan clearance	possibly by inducing topotecan hepatic metabolism	may need to increase topotecan dose during concurrent therapy

SUPPLY AND STORAGE:

***Injection*:**

Sandoz Canada Inc. and Hospira Healthcare Corporation supply topotecan as a solution for injection in 4 mg single-use (preservative free) vials in a concentration of 1 mg/mL. Refrigerate. Protect from light.[32,33]

Mylan Pharmaceuticals supplies topotecan as 4 mg vials of sterile lyophilized powder. Store at room temperature. Protect from light.[34]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***over 30 min***
Continuous infusion	investigational, over 24 h[22,35]
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	is being studied in clinical trials in children[36]
Intra-arterial	no information found
Intravesical	no information found

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:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 weeks***:	***1.5 mg/m^2*** (range 0.75-2 mg/m^2) ***IV once daily for 5 consecutive days starting on day 1*** (***total dose per cycle 7.5 mg/m^2*** [range 3.75-10 mg/m^2])[9,13]
	3-4 weeks:	1.25 mg/m^2/day IV over 24 hours for 5 consecutive days (total dose per cycle 6.25 mg/m^2)[20]
	4-6 weeks:	2 mg/m^2/day (range 1-2 mg/m^2/day) IV over 24 hours for 5 consecutive days starting on day 1 every 4-6 weeks until remission, then every 4-8 weeks (total dose per cycle 10 mg/m^2 [range 5-10 mg/m^2])[22,23]

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure[9]:

CrCl (mL/min)	Dose (mg/m^2)
40-60	1.5 (100%)
20-39	0.75 (50%)
< 20	not recommended

$$\text{CrCl (mL/min)} = \frac{\text{N* x (140 - Age) x weight (kg)}}{\text{serum creatinine (μmol/L)}}$$

*where N = 1.04 for females and 1.23 for males

Dosage in hepatic failure: No adjustment required for total bilirubin < 170 μmol/L[9]; no information found for total bilirubin > 170 μmol/L.

Dosage in dialysis: no information found

Children:

	Cycle Length:	
Intravenous:	3 weeks:	2 mg/m^2/day (range 1.5-2 mg/m^2/day) IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 10 mg/m^2 [range 7.5-10 mg/m^2])[27]

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