Drug Monograph

A - Drug Name

topotecan

SYNONYM(S): hycamptamine

COMMON TRADE NAME(S): Hycamtin®

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B - Mechanism of Action and Pharmacokinetics

Topotecan is a semi-synthetic analogue of camptothecin, an agent derived from the Oriental yew tree, *Camptotheca accuminata*. The cytotoxic effects of the camptothecins are believed to be related to their activity as inhibitors of topoisomerase – I, an enzyme involved in the replication and repair of nuclear DNA. As DNA is replicated in dividing cells, topoisomerase-I acts by binding to super-coiled DNA and causing single-stranded breaks in that DNA. As a result, topoisomerase –I is able to relieve the torsional stresses that are introduced into DNA ahead of the replication complex or moving replication fork. Topotecan binds to the DNA and the topoisomerase complex and prevents religation of DNA strand breaks, leading to cell death.

Absorption	Oral: 42 %	
Distribution	Topotecan is evenly distributed between blood cells and plasma. Pharmacokinetics are dose proportional.	
	Cross blood brain barrier?	Yes
	PPB	35 %
Metabolism	Topotecan undergoes pH-dependent hydrolysis at pH of 4 or less to create an active lactone form, with the equilibrium favouring the ring-opened hydroxyacid form at physiologic pH. It is also metabolized in the liver to N-desmethyl topotecan.	
	Active metabolites	Lactone form, n-desmethyl metabolite

	Inactive metabolites	Hydroxyacid form, n-desmethyl metabolite, glucuronides
Elimination	Topotecan is eliminated primarily in the urine with some elimination via the biliary route.	
	Urine	51% unchanged within 9 days, along with some metabolites
	Half-life	(terminal) : 2-3 hours (IV)

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C - Indications and Status

Health Canada Approvals:

- For the treatment of metastatic cancer of the ovary after failure of initial or subsequent therapy
- For the treatment of sensitive (relapsed ≥ 60 days after first-line chemotherapy) small cell lung cancer after failure of first-line chemotherapy

Other Uses:

- Cervical cancer
- Ewing's sarcoma
- Soft tissue sarcoma

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Minimal

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Alopecia (49%)	E
	Rash (16%) (may be severe)	I E
Gastrointestinal	Abdominal pain (22%)	E

	Anorexia (19%)	I
	Constipation (29%)	E
	Diarrhea (32%)	E
	GI obstruction (5%) (reported in ovarian cancer patients)	E
	Mucositis (18%)	E
	Nausea, vomiting (64%)	I
	Typhlitis (rare)	E
General	Fatigue (29%)	E
	Pain (23%)	E
Hematological	Myelosuppression ± infection, bleeding (grade 4: 78%)	E
Hepatobiliary	↑ LFTs (8%) (2% severe)	E
Hypersensitivity	Hypersensitivity	I
Musculoskeletal	Muscle weakness (5%)	E
	Musculoskeletal pain (5%)	E
Nervous System	Headache (18%)	E
	Paresthesia (7%)	E
Respiratory	Cough, dyspnea (22%)	I E
	Pneumonitis (rare)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for topotecan include nausea, vomiting, alopecia, diarrhea, constipation, fatigue, pain, abdominal pain, cough, dyspnea, anorexia and headache.

Prophylactic use of antiemetics was not routine in patients treated with topotecan.

Myelosuppression is the dose-limiting toxicity of topotecan, particularly neutropenia, which occurs more frequently and is often more severe than thrombocytopenia. It is dose-related, reversible and non-cumulative, but complicated by infection or fever in 23% of patients and 7% of cycles. Neutropenia is more severe in heavily pre-treated patients. Decreased renal function is associated with a lower MTD and more marked neutropenia. **Neutropenic colitis** (typhlitis/caecitis) have been reported in clinical trials.

For patients who present with cough, fever, dyspnea and/or hypoxia suggestive of **interstitial lung disease** (ILD), treatment should be interrupted and patients should be managed accordingly. If ILD is diagnosed, topotecan should be discontinued.

Most of the non-hematologic toxicities are mild to moderate in severity and not dose-limiting.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist depending on disease, response and concomitant therapy; doses may be lower for combination regimens. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Adults:

Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of ≥ 1.5 x 10^9/L, a platelet count of > 100 x 10^9/L, and a hemoglobin level of ≥90 g/L.

Intravenous: 1.5 mg/m² over 30 minutes Days 1 to 5 every 3 weeks

Dosage with Toxicity:

Dose levels: 1.5 mg/m^2, 1.25 mg/m^2, 1 mg/m^2

Worst Toxicity Previous Cycle	Action[1]
Grade 4 neutropenia ≥ 7 days	Reduce dose by 1 dose level OR Use G-CSF with next cycle
Febrile neutropenia	
Cycle delay for hematologic toxicity	
Platelets <25 x 10^9/L	Reduce dose by 1 dose level

Grade 3 GI or organ toxicity	Reduce dose by 1 dose level
Symptoms suggestive of pneumonitis	Hold and manage patient appropriately. Discontinue if confirmed.
Grade 4 GI or organ toxicity	Discontinue
1. Do not retreat until neutrophils ≥ 1 x 10^9/L, platelets ≥ 100 x 10^9/L, hemoglobin ≥90 g/L (after transfusion if necessary) and other toxicity ≤ grade 2.	

Dosage with Hepatic Impairment:

No dosage adjustment is required for treating patients with bilirubin < 171 µmol/L. Total topotecan clearance in patients with hepatic impairment only decreased by about 10%, as compared to the control group of patients.

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Adjusted dose
40-60	no change
20-39	0.75mg/m2
<20	contraindicated

Dosage in the elderly:

No dosage adjustment needed other than for renal function as above.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Mix in 50mL-100mL minibag (NS or D5W); infuse over 30 minutes.
- Final concentration should be between 0.02 mg/mL to 0.5 mg/mL.

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G - Special Precautions

Contraindications:

- Patients with hypersensitivity to topotecan or any of its excipients
- Patients with pre-existing severe myelosuppression
- Patients with severe renal impairment (CrCl <20 mL/min)

Other Warnings/Precautions:

- Use with caution in patients with risk factors for pneumonitis

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Yes
- Mutagenicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
  Topotecan is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.

- Excretion into breast milk: Yes
  Breastfeeding is not recommended.

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H - Interactions

In vitro, topotecan did not inhibit CYP1A2, 2A6, 2C8/9, 2C19, 2D6, 2E, 3A or 4A.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cisplatin when given on day 1	↑ Severity of myelosuppression	Additive	Avoid or reduce doses of cisplatin and topotecan
G-CSF (concomitant)	Prolong duration of neutropenia		If G-CSF is to be used, it should not be initiated until day 6 of the course of therapy.
Curcumin (Tumeric)	May reduce effect of topotecan	Inhibits topotecan induced apoptosis	Avoid concomitant use
Phenytoin	↓ effect of topotecan	↑ clearance of Topotecan, due to possible ↑ in metabolism	Avoid or may need to increase topotecan dose
Docetaxel when given on day 4 of topotecan treatment	50% decrease in docetaxel clearance	Topotecan may change docetaxel metabolism by CYP3A4 inhibition	Give docetaxel on day 1 of topotecan treatment

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Liver and renal function tests	Baseline and at each visit
Clinical toxicity assessment of GI, skin, infection, bleeding and pulmonary effects.	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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