Topotecan:

Class:

- Antineoplastic Agent, Camptothecin; Antineoplastic Agent, Topoisomerase I Inhibitor

Indications:

- **Cervical cancer:** Treatment of recurrent or resistant (stage IVB) cervical cancer (in combination with cisplatin)
- **Ovarian cancer:** Treatment of metastatic ovarian cancer
- **Small cell lung cancer (SCLC):** Treatment of relapsed or refractory SCLC

Unlabeled use :

- Treatment of acute myeloid leukemia (induction in older adults),
- central nervous system lesions (metastatic from lung cancer),
- central nervous system lymphoma (primary),
- Ewing's sarcoma,
- merkel cell cancer,
- osteosarcoma,
- rhabdomyosarcoma (pediatrics),
- neuroblastoma (pediatrics)

Available dosage form in the hospital:

- 4 mg / vial

Trade Names:

- Hycamtin , Oncotecam , Oncotecan , Topodria , Topokebir , Topotel

Dosage: **Note:** Baseline neutrophil count should be $\geq 1500/mm^3$ and platelets should be $\geq 100,000/mm^3$ prior to treatment; for retreatment, neutrophil count should be $>1000/mm^3$; platelets $>100,000/mm^3$ and hemoglobin ≥ 9 g/dL:

-Cervical cancer, recurrent or resistant: IVPB: 0.75 mg/m^2/day for 3 days (followed by cisplatin on day 1 only, [with hydration]) every 21 days

-Ovarian cancer, metastatic: IVPB: 1.5 mg/m^2/day for 5 consecutive days every 21 days, minimum of 4 cycles recommended in the absence of tumor progression **or** (weekly administration; unlabeled dosing) 4 mg/m^2 on days 1, 8, and 15 every 28 days until disease progression or unacceptable toxicity or a maximum of 12 months (Sehouli, 2011)

-Small cell lung cancer (SCLC), relapsed or refractory:

-IVPB: 1.5 mg/m^2/day for 5 consecutive days every 21 days, minimum of 4 cycles recommended in the absence of tumor progression

-Oral: 2.3 mg/m^2/day for 5 consecutive days every 21 days (round dose to the nearest 0.25 mg); if patient vomits after dose is administered; do not give a replacement dose.

Geriatric

Refer to adult dosing.

Renal Impairment:

****Manufacturer's recommendations:**

I.V.:

- Cl_{cr} ≥40 mL/minute: No dosage adjustment necessary.
- Cl_{cr} 20-39 mL/minute: Reduce dose to 0.75 mg/m^2/dose
- Cl_{cr} <20 mL/minute: No dosage adjustment provided in manufacturer's U.S. labeling (insufficient data available for dosing recommendation); use is contraindicated in the Canadian labeling.

Note: For topotecan in combination with cisplatin for cervical cancer, do not initiate treatment in patients with serum creatinine >1.5 mg/dL; consider discontinuing treatment in patients with serum creatinine >1.5 mg/dL in subsequent cycles.

Oral:

- Cl_{cr} ≥50 mL/minute: No dosage adjustment necessary.
- Cl_{cr} 30-49 mL/minute: Reduce dose to 1.8 mg/m^2/day
- Cl_{cr} <30 mL/minute: No dosage adjustment provided in manufacturer's U.S. labeling (insufficient data available for dosing recommendation).

Alternate recommendations:

Aronoff, 2007: I.V.:

Adults:

- Cl_{cr} >50 mL/minute: Administer 75% of dose
- Cl_{cr} 10-50 mL/minute: Administer 50% of dose
- Cl_{cr} <10 mL/minute: Administer 25% of dose

Hemodialysis: Avoid use

Continuous ambulatory peritoneal dialysis (CAPD): Avoid use

Continuous renal replacement therapy (CRRT): 0.75 mg/m^2

Kintzel, 1995: I.V.:

- Cl_{cr} 46-60 mL/minute: Administer 80% of dose
- Cl_{cr} 31-45 mL/minute: Administer 75% of dose
- Cl_{cr} ≤30 mL/minute: Administer 70% of dose

Hepatic Impairment:

****Manufacturer's labeling:**

I.V.: Bilirubin 1.7-15 mg/dL (U.S. labeling) or >1.5 - <10 mg/dL (Canadian labeling): No dosage adjustment necessary (the half-life is increased slightly; usual doses are generally tolerated).

Oral: Bilirubin >1.5 mg/dL: No dosage adjustment necessary.

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of

full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

1. Cervical cancer (cisplatin may also require dosage adjustment): I.V.: Severe febrile neutropenia (<1000/mm^3 with temperature of 38°C) or platelet count <25,000/mm^3: Reduce topotecan to 0.6 mg/m^2/day for subsequent cycles (may consider G-CSF support [beginning on day 4] prior to instituting dose reduction for neutropenic fever.

For neutropenic fever despite G-CSF use, reduce dose to 0.45 mg/m^2/day for subsequent cycles.

2. Ovarian cancer: I.V.: Dosage adjustment for hematological effects: Severe neutropenia (<500/mm^3) or platelet count <25,000/mm^3: Reduce dose to 1.25 mg/m^2/day for subsequent cycles (may consider G-CSF support [beginning on day 6] prior to instituting dose reduction for severe neutropenia). **Note:** The Canadian labeling states that the dose may be further reduced to 1 mg/m^2/day if necessary.

3. Small cell lung cancer (SCLC):

I.V.: Dosage adjustment for hematological effects: Severe neutropenia (<500/mm^3) or platelet count <25,000/mm^3: Reduce dose to 1.25 mg/m^2/day for subsequent cycles (may consider G-CSF support [beginning on day 6] prior to instituting dose reduction for severe neutropenia). **Note:** The Canadian labeling states that the dose may be further reduced to 1 mg/m^2/day if necessary.

Oral: Severe neutropenia (neutrophils <500/mm^3 associated with fever or infection or lasting ≥7 days) or prolonged neutropenia (neutrophils ≥500/mm^3 to ≤1000/mm^3 lasting beyond day 21) or platelets <25,000/mm^3 or grades 3/4 diarrhea: Reduce dose by 0.4 mg/m^2/day for subsequent cycles (may consider same dosage reduction for grade 2 diarrhea if clinically indicated).

Common side effect:

- Central nervous system: Fatigue (6% to 29%), fever (5% to 28%), pain (5% to 23%), headache (18%)
- Dermatologic: Alopecia (10% to 49%), rash (16%)
- Gastrointestinal: Nausea (8% to 64%), vomiting (10% to 45%), diarrhea (6% to 32%; Oral: grade 3: 4%; grade 4: ≤1%; onset: 9 days), constipation (5% to 29%), abdominal pain (5% to 22%), anorexia (7% to 19%), stomatitis (18%)
- Hematologic: Anemia (89% to 98%; grade 4: 7% to 37%; nadir: 15 days), neutropenia (83% to 97%; grade 4: 32% to 80%; nadir 12-15 days; duration: 7 days), leukopenia (86% to 97%; grade 4: 15% to 32%), thrombocytopenia (69% to 81%; grade 4: 6% to 27%; nadir: 15 days; duration: 3-5 days), neutropenic fever/sepsis (2% to 43%)
- Neuromuscular & skeletal: Weakness (3% to 25%)
- Respiratory: Dyspnea (6% to 22%), cough (15%)
- Miscellaneous: Infection (≤17%)

Pregnancy Risk Factor: D