TOPOISOMERASE I – TARGETING DRUGS

IRINOTECAN (CPT-11)
(CAMPTOSAR®)

I. MECHANISM OF ACTION

A) Molecule consists of a 5-ring structure with ring five containing a lactone that is essential for activity.
B) Irinotecan is a prodrug for the active form SN-38. Carboxylesterases in serum and tissues convert irinotecan to SN-38. Conversion rate shows genetic variability.
C) Inhibits topoisomerase I. Topo I relaxes supercoiled double stranded DNA. Topo I concentrations are relatively constant throughout the cell cycle.
D) SN-38 binds to DNA and topo I together until the DNA replication fork reaches the so-called cleavable complex and causes double-stranded DNA break. SN-38 has 100 times the affinity of irinotecan for topo I.
E) Resistance occurs as a result of mutations of topoisomerase I, reduced concentrations of topo I, lack of carboxylesterase activity, or decreased intracellular retention.
F) Radiation sensitizer.
G) Schedule dependent activity-S phase.

II. PHARMACOKINETICS

A) Not available orally.
B) Extensive (88-94%) binding by SN-38 to albumin. Distributes to bile, saliva, sweat, and pleural fluid.
C) SN-38 is glucuronidated and eliminated in the bile. Gut flora may convert SN-38 glucuronide to SN-38 and through enterohepatic recirculation; the active form may be reabsorbed. Failure to glucuronidate the molecule or reconversion back to SN-38 may lead to late onset diarrhea.
D) Irinotecan and its metabolites are excreted primarily in the bile and feces, and to a smaller extent through the kidneys.
E) The terminal half-life for irinotecan and SN-38 is 6-12 hours and 10-20 hours respectively.

III. DOSAGE AND ADMINISTRATION

A) Administered as a short infusion over 30-90 minutes once every 3 weeks or weekly.
B) In clinical trials, irinotecan was not administered to patients with serum bilirubin greater than 2 mg/dL or serum transaminases greater than 3 times the upper limit of normal in patients without liver metastasis or serum transaminases greater than 5 times the upper limit of normal in patients with liver metastasis.

Irinotecan Dosage Adjustment for Patients with Hepatic Dysfunction and Previous Abdominal or Pelvic Irradiation		
	Recommended initial dose, monotherapy	
Serum bilirubin	Once-weekly regimen	Every 21 day regimen
< 1 mg/dL	125 mg/m^2	350 mg/m^2
1 – 2 mg/dL	100 mg/m^2	300 mg/m^2
> 2 mg/dL	Not recommended	Not recommended

Reference: Facts and Comparisons, Cancer Chemo Manual; Accessed 3/25/05.

IV. TOXICITY

A) Diarrhea is the dose limiting adverse event. It can occur early (within 1-6 hours of dose) due to inhibition of acetylcholinesterase and is responsive to oral or SC atropine (occurs in 51% patients). Subsequent episodes of this event are tempered with prophylactic ondansetron or diphenhydramine. Later onset diarrhea (occurring in 30% patients) is due to mucosal damage and requires aggressive loperamide dosing (4 mg initially followed by 2 mg every 2 hours up to 24 mg daily. Continue for at least 12 hours after cessation of diarrhea). Late onset diarrhea occurs with the 2nd or 3rd course of weekly therapy or day 6 of the 21-day cycle. [Reference: Sargent DJ, et al. *N Engl J Med* 2001;345:144 - 5].

Recommendations for dose modification based on GI toxicity:

(a) Combination schedules:

Grade	**During a course of therapy**	**At the start of the next course of therapy (after adequate recovery) compared to the starting dose in the previous course**
1 (2 - 3 stools/day > pretreatment)	Delay dose until resolved to BL, then maintain dose level	Maintain dose level
2 (4 - 6 stools/day > pretreatment)	Omit dose until resolved to BL, then ↓ one dose level	Maintain dose level
3 (7 - 9 stools/day > pretreatment)	Omit dose until resolved to BL, then ↓ 1 dose level	↓ One dose level
4 (≥ 10 stools/day > pretreatment)	Omit dose to until resolved to BL, then ↓ 2 dose levels	↓ Two dose levels

Combination with 5-FU: normal dose for weekly regimen is 125 mg/m^2; Adjusted dose level 1 = 100 mg/m^2 and Adjusted dose level 2 = 75 mg/m^2
Reference: LexiComp Drug Information Handbook 2003 - 2004 (11th Edition).

(b) Single-agent schedule:

Grade	**During a course of therapy**	**At the start of the next course of therapy (after adequate recovery) compared to the starting dose in the previous course**	
	Weekly	Weekly	Once every 3 weeks
1 (2 - 3 stools/day > pretreatment)	Maintain dose level	Maintain dose level	Maintain dose level
2 (4 - 6 stools/day > pretreatment)	↓ 25mg/m^2	Maintain dose level	Maintain dose level
3 (7 - 9 stools/day > pretreatment)	Omit dose, then ↓ 25mg/m^2 when resolved to ≤ grade 2	↓ 25mg/m^2	↓ 50mg/m^2
4 (≥ 10 stools/day > pretreatment)	Omit dose, then ↓ 50mg/m^2 when resolved to ≤ grade 2	↓ 50mg/m^2	↓ 50mg/m^2

Normal dose for weekly regimen is 125 mg/m^2; Adjusted dose level 1 = 100 mg/m^2 and Adjusted dose level 2 = 75 mg/m^2; Q21D regimen: BL dose is 350 mg/m^2 q3weeks; Adjusted dose level 1 = 300 mg/m^2; Adjusted dose level 2 = 250 mg/m^2
Reference: LexiComp Drug Information Handbook 2003 - 2004 (11th edition).

B) Neutropenia – dose related. Dosing every 3 weeks has higher incidence than weekly. (Severe neutropenia in 47–78% of patients). Nadir 15 days; recovery 24 – 28 days. Patients with prior pelvic or abdominal DXRT have an increased incidence of Grade III/IV neutropenia.

ANC	Single-agent regimens	Combination regimens
1 – 4.9 x 10^9/L	↓ Dose by 25 mg/m^2 for current cycle. Return to original dose for subsequent cycles.	↓ Dose for current cycle. No change in dose for subsequent cycles. Once-weekly regimen: ↓ dose by 25% for current cycle. Q2W regimen: ↓ dose by 30 mg/m^2 for current cycle.
0.5 – 0.999 x 10^9/L	Omit dose. Resume therapy when ANC greater than 1 x 10^9/L. Once weekly regimen: ↓ dose by 25 mg/m^2 for subsequent cycles. Every 21 day regimen: ↓ dose by 50 mg/m^2 for subsequent cycles.	Omit dose. Resume therapy when ANC greater than 1 x 10^9/L. Once weekly regimen: ↓ dose by 25 mg/m^2 for current and subsequent cycles. Q2W regimen: ↓ dose by 30 mg/m^2 for current and subsequent cycles.
< 0.5 x 10^9/L	Omit dose. When ANC greater than 1 x 10^9/L, ↓ dose by 50 mg/m^2 for current and subsequent cycles.	Omit dose. Resume when ANC greater than 1 x 10^9/L. Once weekly regimen: ↓ dose by 50 mg/m^2 for current and subsequent cycles. Q2W regimen: ↓ dose by 60 mg/m^2 for current and subsequent cycles.
Neutropenic fever (ANC < 0.5 x 10^9/L+ Temperature ≥ 100.5^{o}C	Omit dose. When fever resolves and ANC greater than 1 x 10^9/L, ↓ dose by 50 mg/m^2 for current and subsequent cycles.	Omit dose. When fever resolves and ANC greater than 1 x 10^9/L, resume therapy. Once-weekly regimen: ↓ dose by 50 mg/m^2 for current and subsequent cycles. Q2W regimen: ↓ dose by 60 mg/m^2 for current and subsequent cycles.

C) Moderately emetogenic (35–60%).
D) Alopecia (40%).
E) Mucositis.
F) In Japanese trials only, an acute pulmonary toxicity was seen. The chest X-ray had a reticulonodular air pattern and the patient had fever, dyspnea, and eosinophilia.

V.CLINICAL MONITORING: CBC baseline and prior to each cycle; LFT's

The active form of irinotecan, SN-38, is metabolized by the polymorphic enzyme UGT1A1. UTG1A1 activity is reduced in patients with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Patients with reduced UGT1A1 activity are at an increased risk of experiencing grade 4 neutropenia while being treated with irinotecan. The FDA approved a diagnostic test to detect the UGT1A1*1 (normal) and the UGT1A1*28 (variant alleles). The test is conducted using peripheral blood. The Irinotecan package insert has been amended to recommend a lower starting dose of irinotecan for patients whoa re homozygous for the UGT1A1*28 allele and indicates an increased risk for neutropenia for patients with UGT1A1 activity. This test is manufactured by Third Wave Technologies. Contact details are: 608-273-8933 or 1-888-898-2357 or www.twt.com.

VI.DRUG INTERACTIONS

Ask patients about herbal medications. St Johns Wort was reported at the 2002 ASCO meeting to enhance metabolism of irinotecan a 50% reduction in the systemic exposure (AUC) of irinotecan compared to irinotecan with no St Johns Wort.

Ketoconazole: shown to reduce the metabolism of irinotecan leading to a 4-fold higher exposure to irinotecan - greater toxicity [Reference: Kehrer DF, et al. *J Clin Oncol* 2002; 14:3122 - 9].

TOPOTECAN
(HYCAMTIN®)

I. MECHANISM OF ACTION

A) Molecule consists of a 5-ring structure with ring five containing a lactone that is essential for activity.
B) Inhibits topoisomerase I. Topo I relaxes supercoiled double stranded DNA. Topo I concentrations are relatively constant throughout the cell cycle.
C) Topotecan binds to DNA and topo I together until the DNA replication fork reaches the so-called cleavable complex and causes double-stranded DNA break.
D) Resistance occurs as a result of mutations of topoisomerase I or decreased intracellular retention.
E) Radiation sensitizer.
F) Schedule dependent activity. S-phase specific.

II. PHARMACOKINETICS

A) Oral bioavailability is 32% (20 - 59% range).
B) Undergoes rapid intravascular hydrolysis of the lactone ring to form the carboxylate.
C) Distribution is large with CSF concentrations 29% of plasma concentrations.
D) Elimination occurs by renal elimination of the carboxylate.

III. DOSAGE AND ADMINISTRATION

A) Administered as a short infusion once daily for 5 days every 3-4 weeks for ovarian cancer.
B) Given as a continuous infusion to treat myelodysplastic syndrome and acute leukemia in investigational protocols.
C) Mix in D_5W to preserve lactone structure (active form).

IV. TOXICITY

A) Non-cumulative, reversible neutropenia is the dose-limiting adverse event. This reaction occurs regardless of schedule.
B) Mucositis is occasionally severe.
C) Less commonly patients experience emesis, diarrhea, fever, alopecia, rash, and elevated liver function tests.