Irinotecan

Class: Camptothecin

Indications :

_Cervical cancer

_CNS tumor

_Esophageal cancer

_Ewing's sarcoma

_Gastric cancer

_Nonsmall cell lung cancer

_Pancreatic cancer

_Small cell lung cancer

_Colorectal cancer

Available dosage form in the hospital:40 MG , 100 MG VIAL

Trade name : Camptosar

Doses: **Note:** A reduction in the starting dose by one dose level should be considered for prior pelvic/abdominal radiotherapy, performance status of 2, or known homozygosity for UGT1A1*28 allele. Consider premedication of atropine 0.25-1 mg I.V. or SubQ in patients with cholinergic symptoms (eg, increased salivation, rhinitis, miosis, diaphoresis, abdominal cramping) or early onset diarrhea. Details concerning dosage in combination regimens should also be consulted.

-Colorectal cancer, metastatic (single-agent therapy): I.V.:

-Weekly regimen: 125 mg/m^2 over 90 minutes on days 1, 8, 15, and 22 of a 6-week treatment cycle (may adjust upward to 150 mg/m^2 if tolerated)

- Adjusted dose level -1: 100 mg/m^2
- Adjusted dose level -2: 75 mg/m^2
- Further adjust to 50 mg/m^2 (in decrements of 25-50 mg/m^2) if needed

-Once-every-3-week regimen: 350 mg/m^2 over 90 minutes, once every 3 weeks

- Adjusted dose level -1: 300 mg/m^2
- Adjusted dose level -2: 250 mg/m^2
- Further adjust to 200 mg/m^2 (in decrements of 25-50 mg/m^2) if needed

-Colorectal cancer, metastatic (in combination with fluorouracil and leucovorin): I.V.: Six-week (42-day) cycle:

-Regimen 1: 125 mg/m^2 over 90 minutes on days 1, 8, 15, and 22; to be given in combination with bolus leucovorin and fluorouracil (leucovorin administered immediately following irinotecan; fluorouracil immediately following leucovorin)

- Adjusted dose level -1: 100 mg/m^2
- Adjusted dose level -2: 75 mg/m^2
- Further adjust if needed in decrements of ~20%

-Regimen 2: 180 mg/m^2 over 90 minutes on days 1, 15, and 29; to be given in combination with infusional leucovorin and bolus/infusion fluorouracil (leucovorin administered immediately following irinotecan; fluorouracil immediately following leucovorin)

- Adjusted dose level -1: 150 mg/m^2
- Adjusted dose level -2: 120 mg/m^2
- Further adjust if needed in decrements of ~20%

-Colorectal cancer, metastatic (unlabeled dosing): I.V.: FOLFOXIRI regimen: 165 mg/m^2 over 1 hour once every 2 weeks

-Cervical cancer, recurrent or metastatic (unlabeled use): I.V.: 125 mg/m^2 over 90 minutes once weekly for 4 consecutive weeks followed by a 2-week rest during each 6 week treatment cycle

-CNS tumor, recurrent glioblastoma (unlabeled use): I.V.: 125 mg/m^2 over 90 minutes once every 2 weeks (in combination with bevacizumab). **NOTE:** in patients taking concurrent antiepileptic enzyme-inducing medications irinotecan dose was increased to 340 mg/m^2

-Esophageal cancer, metastatic or locally advanced (unlabeled use): I.V.: 65 mg/m^2/dose over 90 minutes days 1, 8, 15, and 22 of a 6-week treatment cycle (in combination with cisplatin) (Ajani, 2002; Ilson, 1999)**or** 80 mg/m^2/dose weekly for 6 weeks of a 7-week treatment cycle (in combination with leucovorin and fluorouracil) **or** 250 mg/m^2/dose every 3 weeks (in combination with capecitabine)

-Ewing's sarcoma, recurrent or progressive (unlabeled use): I.V.: 20 mg/m^2/dose days 1-5 and days 8-12 every 3 weeks (in combination with temozolomide)

-Gastric cancer, metastatic or locally advanced (unlabeled use): I.V.: 65 mg/m^2/dose over 90 minutes days 1, 8, 15, and 22 of a 6-week treatment cycle (in combination with cisplatin) (Ajani, 2002) **or** 180 mg/m^2/dose over 90 minutes every 2 weeks (in combination with leucovorin and fluorouracil) (Bouche, 2004) **or** 80 mg/m^2/dose weekly for 6 weeks of a 7-week treatment cycle (in combination with leucovorin and fluorouracil) (Dank, 2008) **or** 250 mg/m^2/dose every 3 weeks (in combination with capecitabine)

-Nonsmall cell lung cancer, advanced (unlabeled use): I.V.: 60 mg/m^2 days 1, 8, and 15 every 4 weeks (in combination with cisplatin)

-Pancreatic cancer, advanced (unlabeled use): I.V.: FOLFIRINOX regimen: 180 mg/m^2/dose over 90 minutes every 2 weeks

-Small cell lung cancer, extensive stage (unlabeled use): I.V.: 60 mg/m^2 days 1, 8, and 15 every 4 weeks (in combination with cisplatin) or 65 mg/m^2 days 1 and 8 every 3 weeks (in combination with cisplatin) or 175 mg/m^2 day 1 every 3 weeks (in combination with

carboplatin) or 50 mg/m^2 days 1, 8 and 15 every 4 weeks (in combination with carboplatin) .

Geriatric

-Weekly dosing schedule: No dosing adjustment is recommended

-Every 3-week dosing colorectal cancer schedule: Recommended initial dose is 300 mg/m^2/dose for patients ≥70 years

Renal Impairment:

-Renal impairment: No dosage adjustment provided in manufacturer's labeling (has not been studied); use with caution.

-Dialysis: Use in patients with dialysis is not recommended by the manufacturer; however, literature suggests reducing weekly dose from 125 mg/m^2 to 50 mg/m^2 and administer after hemodialysis or on nondialysis days (Janus, 2010).

Hepatic Impairment:

-*Manufacturer's recommendations:*

- Liver metastases with normal hepatic function: No dosage adjustment necessary.
- Bilirubin >ULN to ≤2 mg/dL: Consider reducing initial dose by one dose level
- Bilirubin >2 mg/dL: Use is not recommended.

-*Alternate recommendations:* The following adjustments have been used by some clinicians:

- Bilirubin 1.5-3 mg/dL: Administer 75% of dose (Floyd, 2006)
- Bilirubin 1.51 to 3 times ULN: Reduce dose from 350 mg/m^2 every 3 weeks to 200 mg/m^{2}every 3 weeks (Raymond, 2002)

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

It is recommended that new courses begin only after the granulocyte count recovers to ≥1500/mm^3, the platelet counts recover to ≥100,000/mm^3, and treatment-related diarrhea has fully resolved. Depending on the patient's ability to tolerate therapy, doses should be adjusted in increments of 25-50 mg/m^2. Treatment should be delayed 1-2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consider discontinuing irinotecan. See tables.

Colorectal Cancer: Single-Agent Schedule: Recommended Dosage Modifications[1]			
Toxicity NCI Grade[2] (Value)	**During a Cycle of Therapy**	**At Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to Starting Dose in Previous Cycle[1]**	
	Weekly	**Weekly**	**Once Every 3 Weeks**
[1]All dose modifications should be based on the worst preceding toxicity.			
[2]National Cancer Institute Common Toxicity Criteria (version 1.0).			
[3]Excludes alopecia, anorexia, asthenia.			
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia			
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic Fever(grade 4 neutropenia and ≥ grade 2 fever)	Omit dose until resolved, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other Hematologic Toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
1 (2-3 stools/day > pretreatment)	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretreatment)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretreatment)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (≥10 stools/day > pretreatment)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other Nonhematologic Toxicities[3]			
1	Maintain dose level	Maintain dose level	Maintain dose level

Colorectal Cancer: Single-Agent Schedule: Recommended Dosage Modifications[1]

Toxicity NCI Grade[2] (Value)	During a Cycle of Therapy	At Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to Starting Dose in Previous Cycle[1]	
	Weekly	Weekly	Once Every 3 Weeks
2	↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
3	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2

Colorectal Cancer: Combination Schedules: Recommended Dosage Modifications[1]

Toxicity NCI[2]Grade (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to the Starting Dose in the Previous Cycle[1]
[1]All dose modifications should be based on the worst preceding toxicity.		
[2]National Cancer Institute Common Toxicity Criteria (version 1.0).		
[3]Excludes alopecia, anorexia, asthenia.		
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	↓ 1 dose level	Maintain dose level
3 (500-999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic Fever(grade 4 neutropenia and ≥ grade 2 fever)	Omit dose until resolved, then ↓ 2 dose levels	
Other Hematologic Toxicities	Dose modifications for leukopenia or thrombocytopenia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretreatment)	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretreatment)	Omit dose until resolved to baseline,	Maintain dose level

Colorectal Cancer: Combination Schedules: Recommended Dosage Modifications[1]		
Toxicity NCI[2]Grade (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to the Starting Dose in the Previous Cycle[1]**
	then ↓ 1 dose level	
3 (7-9 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ by 1 dose level	↓ 1 dose level
4 (≥10 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels
Other Nonhematologic Toxicities		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Mucositis and/or stomatitis	Decrease only 5-FU, not irinotecan	Decrease only 5-FU, not irinotecan

Common side effect :

Cardiovascular: Vasodilation (9% to 11%)

Central nervous system: Cholinergic toxicity (47% - includes rhinitis, increased salivation, miosis, lacrimation, and intestinal hyperperistalsis); fever (44% to 45%), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%)

Dermatologic: Alopecia (46% to 72%)

Endocrine & metabolic: Dehydration (15%)

Gastrointestinal: Diarrhea, late (83% to 88%), diarrhea, early (43% to 51%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), cramps (57%), anorexia (44% to 55%).

Hematologic: Anemia, leukopenia ,thrombocytopenia ,neutropenia

Hepatic: Bilirubin increased (84%), alkaline phosphatase increased (13%)

Neuromuscular & skeletal: Weakness (69% to 76%), back pain (14%)

Respiratory: Dyspnea (22%), cough (17% to 20%), rhinitis (16%)

1% to 10%:

Cardiovascular: Edema (10%), hypotension (6%), thromboembolic events (5%)

Central nervous system: Somnolence (9%), confusion (3%)

Gastrointestinal: Abdominal fullness (10%), dyspepsia (10%)

Hematologic: Neutropenic fever (grades 3/4: 2% to 6%), hemorrhage (grades 3/4: 1% to 5%), neutropenic infection (grades 3/4: 1% to 2%)

Hepatic: AST increased (10%), ascites and/or jaundice (grades 3/4: 9%)

Pregnancy category : D