A NURSE'S GUIDE TO ASSESSING CHEMOTHERAPY-INDUCED DIARRHEA

onivyde®
(irinotecan liposome injection)

INDICATION

ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

- Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment
- Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warnings, for ONIVYDE®.

ABOUT THIS GUIDE

As an oncology nurse, you play a key role in the identification, assessment, and management of **chemotherapy-induced diarrhea (CID)** in your patients.[1,2] CID can significantly impact your patients' quality of life—as well as their continued treatment. Indeed, many patients with CID require dose modifications, alterations, or discontinuation of their chemotherapy.[3]

Asking questions about your patients' symptoms, in addition to using the NCI-CTCAE criteria for diarrhea severity, may help to better characterize their symptoms.

CID is a predictable and well-recognized side effect of ONIVYDE®.[2,3] Patient education is essential, and oncology nurses are key to educating patients—and their caregivers—on the importance of assessing and managing CID.

This guide is intended to help you identify CID in your metastatic pancreatic cancer patients who are taking ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin (LV). This guide is provided for informational purposes only and does not constitute medical advice. This guide is not intended to substitute professional medical advice or replace applicable treatment standards.

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WHY ONIVYDE® CAN CAUSE DIARRHEA

Diarrhea is a common and potentially severe and life-threatening side effect of ONIVYDE®, an encapsulation of **irinotecan** in a long-circulating liposome.[5,6] It is also a common side effect of **fluorouracil (5-FU)**, especially when given with **leucovorin (LV)**.[3]

Irinotecan may cause diarrhea because the active metabolite SN-38 is excreted into the digestive tract, exposing the mucosal tissues of the intestine to its cytotoxic effect. Irinotecan may also increase inflammatory cytokines (such as tumor necrosis factor alpha) which may cause intestinal tissue damage.[3]

IRINOTECAN MAY CAUSE[7,8]:

Early (acute) diarrhea, within the first 24 hours after administration. It:

- is dose-dependent
- usually lasts about 30 minutes
- is a cholinergic response that may frequently be accompanied by abdominal cramping, watery eyes, rhinitis, and/or increased salivation
- can be managed with atropine at onset

Late (delayed) diarrhea, more than 24 hours after administration (typically 6 to 14 days after). It:

- can occur at any dose level
- can be life-threatening, so patient and caregiver education should include notifying MD upon initial onset of delayed diarrhea

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Fluorouracil (5-FU) may cause diarrhea because cells in the digestive tract are exposed to its cytotoxic effect, leading to apoptosis and tissue inflammation. Intestinal tissue damage stimulates secretion of fluid into the intestinal lumen, leading to loose stools.[3]

FLUOROURACIL MAY CAUSE[7,8]:

Diarrhea that is:

- watery and/or bloody
- more severe when **leucovorin (LV)** is added

SELECTED IMPORTANT SAFETY INFORMATION FOR ONIVYDE®

- An individual patient may experience both early- and late-onset diarrhea
- In the ONIVYDE + 5-FU/LV arm (n=117) of a clinical trial:
  - Early diarrhea occurred in 30% (any grade) and 3% (grades 3-4) of patients
  - Late diarrhea occurred in 43% (any grade) and 9% (grades 3-4) of patients

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PHYSICAL EXAM AND LAB EVALUATION CHECKLIST

As an oncology nurse, doing physical examinations and laboratory tests are key to assessing CID in patients.[2] The following is a helpful checklist to use[2]:

Evaluate abdomen

- Abdominal exam—check for tenderness, guarding, rigidity; signs of bloating; presence of bowel sounds
- Perianal or peristomal exam—check skin integrity; look for hemorrhoids or rectal fissures

Evaluate hydration status

- Skin turgor, mucosal/conjunctival moisture, vein filling/emptying
- Changes in orthostatic blood pressure
- Lab tests for electrolytes, blood urea nitrogen, and creatinine

Rule out infection

- Stool culture lab tests to assess for infection (eg, *clostridium difficile*)
- Complete blood count

Educate patients and caregivers

- Review dietary guidelines
- Review any over-the-counter medicines, vitamins, herbal therapies

ASSESSING DIARRHEA USING NCI CRITERIA

The U.S. National Cancer Institute (NCI) ranks diarrhea severity according to a grading system.[4,8] Called the Common Terminology Criteria for Adverse Events (NCI-CTCAE), it defines diarrhea as passing 3 or more unformed stools in a day, and it ranks severity on a scale of 1 to 5.[4,8,9]

NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS[8,9]

Version 5.0 (revised 2017)

GRADE 1	**Increase of less than 4 stools per day over baseline**
GRADE 2	**Increase of 4-6 stools per day over baseline** *Further indications:* • Nocturnal stools • Moderate cramping (not interfering with daily activities)
GRADE 3	**Increase of 7 or more stools per day over baseline** *Further indications:* • Severe cramping and incontinence (interfering with daily activities and self care) *Response:* • Hospitalization
GRADE 4	**Diarrhea with life-threatening consequences** *Further indications:* • Diarrhea that is bloody *Response:* • Urgent intervention
GRADE 5	Death

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DOSE MODIFICATIONS FOR ONIVYDE®

In the event of diarrhea, ONIVYDE® + 5-FU/LV offers a protocol for dose reduction, delay, and discontinuation.[5]

Toxicity	Directions	ONIVYDE® adjustment in patients receiving 70 mg/m²	Patients homozygous for UGT1A1*28 (who are currently receiving 50 mg/m²)
Grade 2 Diarrhea	Withhold ONIVYDE®. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.*		
Grade 3 or 4 Diarrhea	Withhold ONIVYDE®. Initiate loperamide for late-onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤Grade 1, resume ONIVYDE® at a modified dose.	FIRST OCCURRENCE	43 mg/m²
		SECOND OCCURRENCE	35 mg/m²
		THIRD OCCURRENCE	Discontinue ONIVYDE®

**See Section 5.2 of the full Prescribing Information for ONIVYDE®.*

OTHER THINGS TO CONSIDER

Since the NCI grading system primarily determines diarrhea severity based on *frequency*, it doesn't take into account some other important considerations, such as how a patient reports their own symptoms.[1,4]

As an oncology nurse, you are in a unique position to supplement the NCI (or quantitative) method of assessment with patient-reported (or qualitative) assessment.[2]

Assessing CID accurately may help treatment outcomes and prevent complications, which can be important for metastatic pancreatic cancer patients, for whom *every moment matters*.[2,4]

When your patient starts therapy with ONIVYDE® + 5-FU/LV, it's a good idea to tell them to track any diarrhea symptoms they may experience.[1,7]

It is important to inform patients taking ONIVYDE® + 5-FU/LV of the risk of severe diarrhea. Advise patients to contact their healthcare provider if they experience persistent vomiting or diarrhea; black or bloody stools; or symptoms of dehydration such as lightheadedness, dizziness, or faintness.

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- **Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity**

CONTRAINDICATION

- ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction or anaphylaxis to ONIVYDE or irinotecan HCl

WARNINGS AND PRECAUTIONS

- **Severe Neutropenia: See Boxed WARNING.** In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients
- **Severe Diarrhea: See Boxed WARNING.** Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other symptoms of cholinergic reaction) were observed

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Interstitial Lung Disease (ILD):** Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD
- **Severe Hypersensitivity Reactions:** Irinotecan including ONIVYDE can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction
- **Embryo-Fetal Toxicity:** ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 7 months after the last dose of ONIVYDE treatment

ADVERSE REACTIONS

- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%)
- Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; The most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis
- Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia
- ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia
- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%)

IMPORTANT SAFETY INFORMATION (continued)

- The following adverse reactions have been identified during post approval use of ONIVYDE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Hypersensitivity (including Anaphylactic reaction and Angioedema)

DRUG INTERACTIONS

- Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE
- Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy

USE IN SPECIFIC POPULATIONS

- **Pregnancy and Reproductive Potential:** See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after the last dose of ONIVYDE treatment
- **Lactation:** Advise nursing women not to breastfeed during and for 1 month after the last dose of ONIVYDE treatment

Please see accompanying full Prescribing Information, including Boxed Warnings, for ONIVYDE®.

References: 1. Shaw C, Taylor L. *Clin J Oncol Nurs*. 2012;16(4):413-417. **2.** Viele CS. *Semin Oncol Nurs*. 2003;19(4 suppl 3):2-5. **3.** Koselke EA, Kraft S. *J Hematol Oncol Pharm*. 2012;2(4):1-22. **4.** Lui M, Gallo-Hershberg D, DeAngelis C. *Health Qual Life Outcomes*. 2017;15(1):1-12. **5.** ONIVYDE® [package insert]. Basking Ridge, NJ. Ipsen Biopharmaceuticals, Inc.; 2023. **6.** Zhang H. *Onco Targets Ther*. 2016;9:3001-3007. **7.** Stein A, Voigt W, Jordan K. *Ther Adv Med Oncol*. 2010;2(1):51-63. **8.** Cherny NI. *J Pain Symptom Manage*. 2008;36(4):413-423. **9.** US Department of Health and Human Services. Common Terminology Criteria for Adverse Events v5.0; 2017.

NATIONAL CANCER INSTITUTE CRITERIA

NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS[8,9]

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PATIENT QUESTIONNAIRE

When assessing for diarrhea, it is very important to ask your patients questions about their symptoms. Their answers, together with the NCI grading system, can help you make accurate assessments.[1,2,4] The following questionnaire is adapted from the Systemic Treatment-Induced Diarrhea Assessment Tool (STIDAT).[4]

In the past week…

1. Did you have any diarrhea?
   (If the patient's answer is "no", skip question 2 and go to question 3. If their answer is "yes", ask if their diarrhea—at its worst—was minimal or moderate.)
2. How many times a day, on average, did you have diarrhea?
3. How many times a day, on average, did you pass a normal stool?
4. Did you feel you suddenly needed to pass a stool?
5. Did you feel any discomfort in your abdomen?
6. Were there times when you couldn't reach the bathroom to pass a stool?

   Skip question 7 if the patient answered "no" to question 1.
7. What medications have you taken to manage diarrhea?

   (If the patient's answer is "yes", ask how much was used, in total, and if it helped their diarrhea.)

   For questions 8-12, ask the patient to respond to each question on a scale of 0 to 10, with 0 being "no impact" and 10 being "extreme impact".
8. Have your bowel habits affected your ability to do work or daily activities of living?
9. Have your bowel habits affected your energy level?
10. Have your bowel habits affected your mood?
11. Has diarrhea affected your family life?
12. Has diarrhea affected your social life?

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