Cancer Chemotherapy Update

Gefitinib, Fluorouracil, Oxaliplatin, and Leucovorin (IFOX) Regimen for Colorectal Cancer

Alicia S. Chen, PharmD*; Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP;
and J. Aubrey Waddell, PharmD, FAPhA, BCOP

The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net.

Regimen Name: Gefitinib, fluorouracil, oxaliplatin, and leucovorin (IFOX)

Origin of Name: The regimen is named for 3 of the 4 drugs it contains: gefitinib (Iressa), fluorouracil (5-FU), oxaliplatin, and leucovorin. IFOX is also known as FOLFOX (fluorouracil, leucovorin, and oxaliplatin) with gefitinib.

COMMENTS

Gefitinib was originally approved in the United States for treatment of advanced non-small-cell lung cancer (NSCLC); in 2005, distribution was limited based on subsequent data indicating that it was no more effective than best supportive care.¹ In 2012, the drug was withdrawn from the US market.²

Response to gefitinib is dependent on a mutation of the epidermal growth factor receptor (EGFR). This mutation is present predominantly in persons of East Asian origin, females, never smokers, or persons with adenocarcinoma tumors, suggesting that the drug may be beneficial in selected subpopulations of NSCLC.³⁻¹⁰

In patients with colorectal cancer, response does not appear to be related to the EGFR mutation; however, response does correlate with other events such as p21 and p53 expression. Patients lacking expression of p21 are reported to have higher response rates to gefitinib

than patients maintaining p21 expression and a p53 mutation.¹¹ These data suggest there may be a role for gefitinib in selected subpopulations of colorectal cancer.

INDICATIONS

The IFOX regimen (see **Table 1**) has been studied in advanced solid malignancies¹² and as first-line therapy in metastatic,^{13,14} advanced,¹⁵ and refractory^{16,17} colorectal cancer. Current guidelines do not mention the IFOX regimen for treatment of either colon or rectal cancer.^{18,19}

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing fluorouracil, oxaliplatin, and leucovorin and dispensing gefitinib.

A. Fluorouracil

1. Use fluorouracil injection, 50 mg/mL.
2. Bolus: Dispense in a syringe or dilute with 50 to 250 mL of 0.9% sodium chloride injection (NS) or 5% dextrose injection for short (5 to 15 minute) infusion.
3. Continuous infusion:
 - a. Dilute with 250 to 1,000 mL of NS or 5% dextrose in water (D5W) for infusion over 22 hours.
 - b. Fluorouracil may be diluted to a final volume of 60 to 150 mL with bacteriostatic 0.9%

*Dr. Chen is a Clinical Staff Pharmacist at Medstar Montgomery Medical Center, Olney, Maryland. At the time this article was written, she was a student at the University of Maryland at Baltimore School of Pharmacy.

Table 1. Gefitinib, fluorouracil, oxaliplatin, and leucovorin regimen^{13,15,16}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Gefitinib*	250 mg ¹⁵	PO	1-14	3,500 mg
	500 mg ^{13,16}			7,000 mg
Oxaliplatin	85 mg/m ²	IV	1	85 mg/m ²
Leucovorin	200 mg/m ²	IV	1,2	400 mg/m ²
Fluorouracil	400 mg/m ²	IV bolus	1,2	800 mg/m ²
Fluorouracil	600 mg/m ²	IV infusion	1,2	1,200 mg/m ²

*Starting cycle 2

Cycle repeats: every 14 days

Variations

1. Gefitinib 250 mg/day days 1-14; oxaliplatin 100 mg/m² IV day 1; leucovorin 200 mg/m² IV day 1; fluorouracil 400 mg/m² IV bolus day 1; fluorouracil 2,400 mg/m² IV infusion day 1

Repeats every 14 days¹⁴

2. Gefitinib*	Oxaliplatin	Leucovorin	Fluorouracil
250 mg/day	50 mg/m ² IV	500 mg/m ² IV	1,600 mg/m ² IV infusion
250 mg/day	50 mg/m ² IV	500 mg/m ² IV	2,000 mg/m ² IV infusion
500 mg/day	50 mg/m ² IV	500 mg/m ² IV	1,600 mg/m ² IV infusion
500 mg/day	50 mg/m ² IV	500 mg/m ² IV	2,000 mg/m ² IV infusion

*Starting cycle 2

Weekly for 4 weeks every 6 weeks¹⁷

3. Gefitinib*	Oxaliplatin	Leucovorin	Fluorouracil (bolus)	Fluorouracil (infusion)
250 mg/day	70 mg/m ² IV d1	200 mg/m ² IV d1&2	400 mg/m ² IV d1&2	600 mg/m ² IV d1&2
500 mg/day	85 mg/m ² IV d1	200 mg/m ² IV d1&2	400 mg/m ² IV d1&2	600 mg/m ² IV d1&2
500 mg/day	85 mg/m ² IV d1	200 mg/m ² IV d1&2	400 mg/m ² IV d1&2	600 mg/m ² IV d1&2

*Starting cycle 2

Repeats every 14 days¹²

Note: d1 = day 1; d2 = day 2; IV = intravenous; PO = oral.

sodium chloride injection (BNS) for administration by an ambulatory infusion pump.

B. Oxaliplatin

1. Use oxaliplatin injection 5 mg/mL or powder for injection.
2. Reconstitute the powder to a concentration of 5 mg/mL with sterile water for injection or D5W.
3. Dispense in 250 to 500 mL D5W.

C. Leucovorin

1. Use leucovorin injection 10 mg/mL or powder for injection.
2. Reconstitute the powder to a concentration of 20 mg/mL with sterile water for injection, bacteriostatic water for injection, or D5W.
3. Dilute in 100 to 250 mL D5W for infusion.

D. Gefitinib

1. Use gefitinib 250 mg tablets.

2. For patients unable to swallow tablets:

- a. Place the tablet in 4 to 6 ounces of water or a noncarbonated beverage.
- b. Mix gently until the tablet dissolves and the power disperses (about 20 minutes).
- c. Drink the suspension within 60 minutes of mixing.
- d. Rinse the glass with another 4 to 6 ounces of fluid, and drink the mixture.
- e. Administer the suspension through a nasogastric or gastrostomy tube, followed by 4 to 6 ounces of water.

DRUG ADMINISTRATION

- A. Fluorouracil is administered as an intravenous (IV) push injection or short (5 to 15 minute) infusion followed by a 22-hour IV infusion on days 1 and 2.

B. Oxaliplatin is administered as an IV infusion over 2 hours on day 1.

C. Leucovorin is administered as an IV infusion over 2 hours on days 1 and 2.

D. Gefitinib

1. Is given orally (PO) daily starting on day 1 of cycle 2.
2. The dose should be taken at about the same time each day.
3. May be taken with, or without, food.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The IFOX regimen is predicted to cause acute emesis in 30% to 90% of patients.²⁰⁻²⁴ The studies reviewed reported grade 3 nausea or vomiting in 18% to 27% of patients.^{13,16} Prophylactic antiemetic therapy with a steroid and serotonin antagonist is recommended.²¹⁻²⁴ One group suggests that addition of a neurokinin (NK₁) antagonist may be appropriate in some patients.²¹ One of the following regimens is recommended:

1. Ondansetron 8 mg to 16 mg PO, dexamethasone 12 mg PO, given 30 minutes before oxaliplatin.
2. Granisetron 1 mg to 2 mg PO, dexamethasone 12 mg PO, given 30 minutes before oxaliplatin.
3. Dolasetron 100 mg PO, dexamethasone 12 mg PO, given 30 minutes before oxaliplatin.
4. Palonosetron 0.25 mg IV on day 1 only and dexamethasone 12 mg PO, given 30 minutes before oxaliplatin.

If a neurokinin antagonist is used, add aprepitant 125 mg PO to the above regimens.

The antiemetic therapy should continue for at least 3 days. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (greater than 24 hours) use of these agents, making a steroid, or steroid and dopamine antagonist combination, most appropriate for follow-up therapy.²⁵ One of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of IFOX.
2. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ prochlorperazine 10 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of IFOX.
3. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ promethazine 25 to 50 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50

mg PO every 6 hours if needed, starting on day 2 of IFOX.

If a neurokinin antagonist is used, one of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 days, aprepitant 80 mg PO every morning for 2 days, $\pm$ metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of IFOX.
2. Dexamethasone 4 mg PO twice a day for 3 days, aprepitant 80 mg PO every morning for 2 days, $\pm$ prochlorperazine 10 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of IFOX.
3. Dexamethasone 4 mg PO twice a day for 3 days, aprepitant 80 mg PO every morning for 2 days, $\pm$ promethazine 25 to 50 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of IFOX.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.²⁰⁻²⁴ There is no evidence that substituting granisetron for ondansetron in subsequent treatment cycles or increasing the dose, even to very high doses, is effective. This approach is not recommended.²⁵⁻³⁰

B. Breakthrough Nausea and Vomiting²⁰⁻²⁴: Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is recommended:

1. Metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Prochlorperazine 10 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Prochlorperazine 25 mg rectally every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.
4. Promethazine 25 to 50 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

C. Hypersensitivity Precautions: Oxaliplatin is reported to cause hypersensitivity reactions in 8% to 13% of patients, with the incidence of moderate to severe reactions ranging from <1% to 7%. The most common symptoms are flushing and swelling of the face and hands, itching, sweating,

lacrimation, skin rash, hives, rigors, dyspnea, and fever. Such reactions usually occur during the second or subsequent cycles, but one study suggests that the reactions most often occur around cycle 9 or 10.³¹⁻³³

For mild reactions, the oxaliplatin infusion is stopped and an antihistamine and a corticosteroid may be administered. Moderate to severe reactions usually require administration of parenteral corticosteroids. One report suggests that lengthening the oxaliplatin infusion time from 2 to 6 hours reduces the incidence of hypersensitivity reactions and may be appropriate for some patients. Premedication with corticosteroids and antihistamines does not prevent subsequent hypersensitivity reactions.³¹

D. Hematopoietic Growth Factors: Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen have a greater than 20% incidence of febrile neutropenia before prophylactic use of colony stimulating factors (CSFs) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSFs should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of CSFs is not recommended.^{34,35} Since severe (grade 3 or 4) neutropenia was reported in up to 60% of patients, and febrile neutropenia was reported in 0% to 9% of patients, in the trials reviewed,^{13,16} prophylactic use of CSFs may be appropriate in some patients receiving the IFOX regimen.

E. Diarrhea: Diarrhea is a frequent consequence of protracted venous infusion of fluorouracil and is less common with bolus administration. Concomitant administration of leucovorin increases the incidence and severity of fluorouracil-induced diarrhea. Diarrhea is usually mild to moderate, responding to conventional therapy. Occasionally, the problem can be severe or dose-limiting.

Patients should receive a prescription for an anti-diarrheal agent for use at the onset of diarrhea. The standard recommendation is loperamide 4 mg PO at the onset of diarrhea, followed by 2 mg PO every after each unformed stool, or as often as every 2 hours for 24 hours.³⁶ Patients should be counseled to³⁷:

1. Monitor bowel movements.
2. Treat grade 1 or 2 diarrhea (increase of less than 7 stools per day or nocturnal stools) with loperamide and oral rehydration.
3. Immediately seek advice from their physician, pharmacist, or nurse for persistent (>24 hours) grade 1 or 2 diarrhea or grade 3 diarrhea

(increase of ≥ 7 stools per day or incontinence or symptoms of dehydration).

G. Neurotoxicity: Oxaliplatin causes acute neurotoxicity consisting of cold-induced or -exacerbated paresthesias/dysesthesias and muscle contractions. It also causes chronic neurotoxicity that can impair quality of life. Preclinical data suggest that the acute neurotoxicity may be due to oxaliplatin's effects on voltage-dependent sodium channels and/or chelation of intracellular calcium by the oxaliplatin metabolite, oxalate.³⁸

Intravenous infusion of 1 g each of calcium gluconate and magnesium sulfate before and after the oxaliplatin infusion was reported to significantly reduce the incidence of neurotoxicity.³⁹⁻⁴¹ Recent data indicate this is not effective. The use of calcium gluconate and magnesium sulfate is no longer recommended.⁴²

MAJOR TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (<http://ctep.info.nih.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Atrial fibrillation (grade 3 or 4) 2%¹⁶; deep vein thrombosis (grade 3 or 4) 2%¹⁶; dehydration (grade 3 or 4) 22%¹³; thrombosis (grade 3 or 4) 7%¹³.
- B. Central Nervous System:** Syncope (grade 3 or 4) 2%¹³.
- C. Constitutional:** Abdominal pain or cramping (grade 2) 17% to 75%¹⁶; (grade 3) 4%¹³; (grade 3 or 4) 5%¹⁶; asthenia (grade 3 or 4) 4%¹⁶; dyspnea (grade 3 or 4) 2%¹⁶; (grade 3 or 4) 2%¹⁶; fatigue (grade 3 or 4) 4% to 22%^{13,16}.
- D. Dermatologic:** Dermatitis 37%¹⁵ (grade 3 or 4) 2%¹⁵; hand-foot syndrome (grade 3) 4% to 8%¹⁶ (grade 3 or 4) 2%¹³.
- E. Endocrine/Metabolic:** Hypokalemia (grade 3 or 4) 5% to 33%^{13,16}; hyponatremia (grade 3 or 4) 2% to 7%^{13,16}.
- F. Gastrointestinal:** Anorexia (grade 2) 2%¹⁶ (grade 3 or 4) 2% to 7%^{13,16}; diarrhea 65%¹⁵ (grade 3 or 4)

16% to 67%^{13,15,16}; heartburn (grade 2) 2%¹⁶; ileus (grade 3 or 4) 4% to 7%^{13,16}; intestinal perforation (grade 3 or 4) 4%¹⁶; nausea (grade 3) 6%,¹⁶ (grade 3 or 4) 5% to 22%^{13,16}; stomatitis/mucositis 23%,¹⁵ (grade 3 or 4) 4% to 7%,^{13,15,16} (grade 4) 2%¹⁶; vomiting (grade 3 or 4) 4% to 15%.^{13,16}

G. Hematologic: Anemia (grade 3 or 4) 2% to 5%^{13,16}; leukopenia 21%, (grade 3 or 4) 7%¹⁵; neutropenia 60%,¹⁵ (grade 3 or 4) 18% to 60%^{13,15,16}; thrombocytopenia 33%¹⁵; melena (grade 3 or 4) 2%.¹⁶

H. Hepatic: Ascites (grade 3 or 4) 2%¹⁶; elevated aminotransferases 11% to 25%,^{13,15,16} (grade 3 or 4) 4% to 7%.^{15,16}

I. Infection: (grade 3 or 4) 7%.¹³

J. Neurologic: Unspecified neuropathy 25%,¹⁵ (grade 3 or 4) 2%.¹⁵

K. Pulmonary: Pneumonitis (grade 3) 2%.¹⁶

L. Renal: Renal insufficiency (grade 3 or 4) 4%.¹³

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. Aspartate aminotransferase/alanine aminotransferase (AST/ALT)
2. Total bilirubin
3. Serum creatinine
4. Complete blood count (CBC) with differential

B. Prior to Each Treatment

1. CBC with differential

C. Recommended Pretreatment Values: The minimally acceptable pretreatment CBC values required to begin a cycle with full-dose therapy in the protocols reviewed were:

1. Absolute neutrophil count (ANC) greater than or equal to 1,500 cells/mcL.^{13,16}
2. Platelet count greater than or equal to 100,000 cells/mcL.^{13,16}
3. Renal function: Serum creatinine
 - a. Within normal institutional limits.¹³
 - b. Less than or equal to 1.5 times upper limit of normal (ULN).¹⁶
4. Hepatic function
 - a. Serum bilirubin
 - (1) Less than or equal to 1.5 mg/dL.¹³
 - (2) Less than or equal to 1.5 times ULN.¹⁶
 - b. ALT/AST less than or equal to 2.5 times the ULN^{13,16} **or** less than or equal to 5 times the ULN if liver metastases were present.¹⁶

In clinical practice, a pretreatment ANC of 1,000 cells/mcL and platelets of 75,000 cells/mcL are usually considered acceptable.

DOSAGE MODIFICATIONS

A. Renal Function

1. Oxaliplatin: Creatinine clearance greater than 20 mL/minute, give 100% dose.⁴³
2. Fluorouracil: No dosage adjustment required.^{43,44}
3. Leucovorin: No dosage adjustment required.⁴⁴
4. Gefitinib: No dosage adjustment required.⁴⁴

B. Liver Function

1. Oxaliplatin
 - a. No adjustment required.⁴⁴
 - b. ALT/AST greater than 5 times the ULN and less than or equal to 20 times the ULN, reduce dose to 60 or 70 mg/m².¹³
 - c. Dosage adjustments for elevated AST, ALT, and total bilirubin are not required, but regular assessments of liver function to monitor for oxaliplatin-induced hepatic injury are advised.^{45,46}
2. Fluorouracil
 - a. Bilirubin greater than 5 mg/dL, do not give drug.^{43,47}
 - b. Patients with dihydropyrimidine deficiency, do not give drug.⁴³
3. Leucovorin: No dosage adjustment required.⁴³
4. Gefitinib: No dosage adjustment required.⁴⁸

C. Myelosuppression

1. Nadir absolute neutrophil count less than or equal to 500/mm³ or nadir platelet less than or equal to 50,000/mm³
 - a. First episode, reduce oxaliplatin dose by 20%.¹³
 - b. Subsequent episodes¹³
 - (1) Reduce fluorouracil bolus and infusion dose by 20%.
 - (2) Reduce oxaliplatin dose an additional 20%.

D. Diarrhea: Grade ≥ 3

1. Refractory to antidiarrheals, reduce dose of fluorouracil bolus and infusion by 20%.¹³
2. Second episode, reduce gemcitabine dose to 250 mg daily.¹³
3. Third episode, reduce oxaliplatin dose reduction by 20%.¹³

E. Other

1. Oxaliplatin
 - a. Grade 2 peripheral neuropathy affecting function, reduce dose to 65 mg/m².¹³
 - b. Any grade 4 symptom, discontinue the drug.¹³
2. Gefitinib – grade 3 dermatitis
 - a. First episode, reduce dose to 250 mg daily.¹³
 - b. Second episode, discontinue the drug.¹³

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