Cancer Chemotherapy Update

Mitomycin and Fluorouracil With Concurrent Radiation (FUMIR) Regimen for Anal Cancer

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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@aol.com; 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: FUMIR

Origin of name: The regimen is named for the 2 drugs in the regimen, fluorouracil and mitomycin, with concurrent radiation.

INDICATION(S)

The FUMIR regimen (Table 1) is used as primary therapy of nonmetastatic cancer of the anal canal.¹⁻¹⁴ Current guidelines list mitomycin plus fluorouracil administered concurrently with radiation as initial treatment of nonmetastatic anal canal cancer.¹

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing fluorouracil or mitomycin.

A. Fluorouracil

1. Use fluorouracil 50 mg/mL injection.
2. Dilute in 500 to 1,000 mL of 0.9% sodium chloride injection (NS), 5% dextrose injection (D5W), or a saline/dextrose solution for injection.
3. Fluorouracil may be diluted to a final volume of 60 to 150 mL with bacteriostatic 0.9% sodium chloride injection (BNS) for administration by an ambulatory infusion pump.

B. Mitomycin

1. Use mitomycin powder for injection.

2. Dilute with NS, D5W, or sterile water for injection to a concentration of 0.5 to 1 mg/mL.
3. Dispense in a syringe for injection, or dilute in 50 to 100 mL of NS, D5W, or a saline/dextrose solution for infusion.

DRUG ADMINISTRATION

A. Fluorouracil

1. Fluorouracil is administered as a continuous infusion over 4 days.
2. It may be administered as 4 daily 24-hour infusions or as a single 96-hour infusion.

B. Mitomycin

1. Mitomycin is administered as a slow intravenous (IV) push over 3 to 10 minutes or as a short (5 to 15 minute) infusion.
2. Care should be taken to avoid extravasation.

SUPPORTIVE CARE

A. Acute Emesis Prophylaxis: The FUMIR regimen is predicted to cause acute emesis in 10% to 30% of patients on day 1 and less than 10% of patients on days 2 through 4.^{14,15} The studies reviewed reported grade 1 or 2 emesis in 19% of patients.¹² Grade 3 or 4 emesis was reported in 3% to 6% of patients.^{12,13} Appropriate acute emesis prophylaxis includes a corticosteroid or a dopamine receptor antagonist.¹⁴ One of the following regimens is suggested:

1. Dexamethasone 12 mg orally (PO) given 30 minutes before day 1 of FUMIR.

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Table 1. FUMIR regimen^{2,8,10,12}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Fluorouracil	1,000 mg/m ²	CIVI	1-4, 29-32	8,000 mg/m ²
Mitomycin	10 mg/m ²	IV	1, 29	20 mg/m ²

Cycle does not repeat.

Concurrent radiotherapy 1.8 Gy/day 5 times per week for 5 weeks for a total dose of 45 Gy.

Variations

1. Fluorouracil 750 mg/m² daily on days 1-5 and days 29-33, and a single dose of mitomycin 15 mg/m² on day 1 of radiation.³
2. Fluorouracil 1,000 mg/m² daily on days 1-4 and days 29-33, and a single dose of mitomycin 10 to 15 mg/m² on day 1 of radiation.⁴
3. Fluorouracil 200 mg/m²/day by continuous infusion on days 1-26, and a single dose of mitomycin 10 mg/m² on day 1.⁹
4. Fluorouracil 750 mg/m² on days 1-5, and a single dose of mitomycin 15 mg/m² on day 1.¹¹
5. Fluorouracil 200 mg/m² on days 1-26 of radiation sequence 1, 200 mg/m² on days 1-17 of radiation sequence 2, and mitomycin 10 mg/m² on day 1 of each radiation sequence.¹³
6. Regimen above, fluorouracil capped at 1,500 mg per day.^{5,6}
7. Fluorouracil 1,000 mg/m² daily on days 1-4 and mitomycin 10 mg/m² on day 1 of radiation.⁷

Note: CIVI = continuous intravenous infusion; Gy = Gray; IV = intravenous.

2. Metoclopramide 10 to 40 mg PO given 30 minutes before day 1 of FUMIR.
3. Prochlorperazine 10 mg PO given 30 minutes before day 1 of FUMIR.

Should the above regimens be insufficient for acute emesis prophylaxis, a serotonin (5-HT₃) antagonist and corticosteroid combination can be used. The following regimens are recommended:

1. Ondansetron 16 mg to 24 mg and dexamethasone 12 mg, both given PO 30 minutes before day 1 of FUMIR.
2. Granisetron 2 mg and dexamethasone 12 mg, both given PO 30 minutes before day 1 of FUMIR.
3. Dolasetron 100 mg and dexamethasone 12 mg, both given PO 30 minutes before day 1 of FUMIR.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO, both given 30 minutes before day 1 of FUMIR.

B. Breakthrough Nausea and Vomiting¹⁴: Patients should receive an antiemetic prescription to treat breakthrough nausea and vomiting.¹⁴ One of the following regimens is suggested:

1. Metoclopramide 10 to 40 mg PO every 4 to 6 hours ± diphenhydramine 25 to 50 mg every 4 to 6 hours PO as needed.
2. Prochlorperazine 25 mg suppository rectally every 12 hours ± diphenhydramine 25 to 50 mg every 4 to 6 hours PO as needed.
3. Prochlorperazine 10 mg PO every 4 to 6 hours ± diphenhydramine 25 to 50 mg every 4 to 6 hours PO as needed.

4. Promethazine 12.5 to 25 mg PO every 4 to 6 hours ± diphenhydramine 25 to 50 mg every 4 to 6 hours PO as needed.

C. 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.¹⁶

Because febrile neutropenia was reported in 15% to 18% of patients and fatal neutropenic sepsis was reported in 3% of patients treated with the FUMIR regimen, prophylactic use of CSFs may be considered.^{2,12}

D. Diarrhea: Diarrhea is a frequent consequence of protracted venous infusion of fluorouracil and is less common with bolus administration. Diarrhea is usually mild to moderate, responding to conventional therapy. Occasionally the problem can be severe or dose-limiting. In the studies reviewed, grade 2 diarrhea was reported in 15% to 94% of patients, grade 3 diarrhea was reported in 2% to 20% of patients, and grade 4 diarrhea was reported in 1% of patients receiving FUMIR.^{3,9-13}

Patients should receive a prescription for an antidiarrheal 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.¹⁷ Patients should be counseled to¹⁸:

1. Monitor bowel movements.
2. Treat grade 1 or 2 diarrhea (increase of <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, incontinence, or symptoms of dehydration).

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%.

- Cardiovascular:** Cardiac arrhythmias (grade 1 or 2) 2%,¹² (grade 3 or 4) 1%¹²; cardiac failure (all grades) 2%²; cardiovascular dysfunction not requiring discontinuation of therapy (grade 1 or 2) 13%,¹² (grade 3 or 4) 4%¹²; coagulopathy (any) (grade 1 or 2) 1%¹²; hemorrhage (grade 1 or 2) 12%,¹² (grade 3 or 4) 1%¹²; stroke (all grades) 2%.⁴
- Constitutional symptoms:** Pain (grade 1 or 2) 29%,¹² (grade 3 or 4) 24%¹²; unspecified constitutional symptoms (grade 1 or 2) 24 to 59%,¹² (grade 3 or 4) 8 to 10%.¹²
- Dermatologic:** Dermatitis (grade 1 or 2) 4% to 51%,¹¹ (grade 3) 5%¹¹; extravasation causing skin necrosis (all grades) 4%¹¹; genital dermatitis (grade 3) 15%¹³; inguinal dermatitis (grade 3) 5%¹³; moist desquamation (grade 3) 20%⁸; perianal dermatitis (grade 2) 28%⁹; ulcer (all grades) 0.03% to 9%^{8,9}; unspecified skin toxicity (grade 1 or 2) 9% to 42%.^{3,9,10}
- Endocrine:** Endocrine toxicity (any) (grade 1 or 2) 2%.¹²
- Gastrointestinal:** Anorectal soft tissue toxicity (all grades) 21%⁵; bowel occlusion 0.2% (all grades)⁹; diarrhea (grade 1 or 2) 2% to 96%,^{3,10-12} (grade 3 or 4) 2% to 23%^{3,9,11-13}; mucosal reaction (all

grades) 2%³; nausea (grade 1 or 2) 49%,¹² (grade 3 or 4) 3% to 9%^{12,13}; proctitis (grade 1 or 2) 96%,¹¹ (grade 3 or 4) 4% to 8%^{10,11,13}; stomatitis (grade 1 or 2) 36% to 46%,^{11,12} (grade 3 or 4) 2% to 6%^{3,10,11}; vomiting (grade 1 or 2) 19%,¹² (grade 3 or 4) 3% to 6%.^{12,13}

- Genitourinary:** Cystitis (grade 1 or 2) 54%,¹¹ penile necrosis (all grades) 2%,¹⁰ vaginal stenosis (all grades) 12%.⁸
- Hematologic:** Anemia (grade 3 or 4) 19% to 21%^{5,6}; febrile neutropenia (grade 1 to 3) 15%,¹² (grade 3 or 4) 18%¹²; leukopenia (grade 1 or 2) 2% to 13%,^{5,6,9,10} (grade 3 or 4) 2% to 7%^{9,10}; thrombocytopenia (grade 2) 7%,⁹ (grade 3 or 4) 2% to 6%.^{3,5}
- Hepatic:** Hepatic toxicity (any) (grade 1 or 2) 16%,¹² (grade 3 or 4) 2%.¹²
- Hypersensitivity:** Allergic reaction (grade 1 or 2) 2%.¹²
- Infection:** Pneumonia 5%.⁹
- Musculoskeletal:** Musculoskeletal toxicity (any) (grade 1 or 2) 2%,¹² (grade 3 or 4) 1%.¹²
- Neurologic:** Hand-foot syndrome (all grades) 8%¹²; neurologic toxicity (any) (grade 1 or 2) 16%,¹² (grade 3 or 4) 5%.¹²
- Ocular:** Visual toxicity (any) (grade 1 or 2) 1%, (grade 3 or 4) 0.3%.¹²
- Otic:** Unspecified auditory toxicity (grade 1 or 2) 1%.¹²
- Pulmonary:** Pulmonary toxicity (any) (grade 1 or 2) 10%¹², (grade 3 or 4) 3%.¹²
- Renal:** Acute renal failure (all grades) 3%⁸; renal toxicity (any) (grade 1 or 2) 35%,¹² (grade 3 or 4) 3%.¹²
- Treatment-related mortality:** Neutropenic sepsis 3%,² septicemia 2%,³ stroke 2%.⁴

PRETREATMENT LABORATORY STUDIES NEEDED

- Baseline**
 1. Aspartate aminotransferase/alanine aminotransferase (AST/ALT)
 2. Total and conjugated bilirubin
 3. Serum creatinine
 4. Complete blood count (CBC) with differential
- Prior to each treatment**
 1. CBC with differential
- Recommended pretreatment values:** The minimally acceptable pretreatment CBC values required to begin a cycle with full dose therapy in the trials reviewed were:
 1. Absolute granulocyte count:
 - a. Greater than or equal to 1,800 cells/mcL¹²

- b. Greater than or equal to 2,000 cells/mcL^{9,13}
2. Hemoglobin – greater than or equal to 10 g/dL¹²
3. Platelet count – greater than 100,000 cells/mcL^{9,13}
4. Serum creatinine – less than 1.4 mg/dL^{9,13}

In clinical practice, a pretreatment absolute neutrophil count (ANC) of 1,000 cells/mcL and platelet count of 75,000 cells/mcL are usually considered acceptable.

DOSAGE MODIFICATIONS

A. Renal Function

1. Fluorouracil: No adjustment recommended.^{19,20}
2. Mitomycin: No adjustment recommended.^{19,20}

B. Liver Function

1. Fluorouracil: Bilirubin greater than 5 mg/dL, do not give the drug.²⁰⁻²²
2. Mitomycin: No adjustment recommended.^{21,22}

C. Myelosuppression

1. White blood cell count:
 - a. Pretreatment value of 3,000 to 4,000 cells/mcL, reduce fluorouracil dose by 33%.³
 - b. Pretreatment value of 2,000 to 3,000 cells/mcL, reduce fluorouracil dose by 66%.³
 - c. Nadir value of 1,000 to 2,400 cells/mcL, reduce second dose of mitomycin to 7.5 mg/m².²
 - d. Nadir value of less than 1,000 cells/mcL, reduce second dose of mitomycin to 5 mg/m².²
2. Platelet count:
 - a. Pretreatment value of 75,000 to 100,000 cells/mcL, reduce fluorouracil dose by 33%.³
 - b. Pretreatment value of 50,000 to 75,000 cells/mcL, reduce fluorouracil dose by 66%.³
 - c. Nadir value of 50,000 to 85,000 cells/mcL, reduce second dose of mitomycin to 7.5 mg/m².²
 - d. Nadir value of less than 50,000 cells/mcL, reduce dose of mitomycin to 5 mg/m².
 - e. Grade 1 decrease in platelets, discontinue mitomycin permanently.¹³
3. Granulocyte count: Grade 1 decrease in granulocytes, discontinue mitomycin permanently.¹³
4. Neutrophil count: Grade 4 neutropenia or febrile neutropenia, reduce fluorouracil dose by 50%.¹²

D. Diarrhea

1. Grade 3: Discontinue fluorouracil until diarrhea improves to ≤ grade 2.⁹
2. All grades: Discontinue mitomycin.¹³

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