Cancer Chemotherapy Update

Capecitabine and Gemcitabine (CapGem, CG, GemCap) for Advanced Pancreatic and Biliary Tract 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@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: Capecitabine and Gemcitabine (CapGem, CG, GemCap)

Origin of Name: Acronym for the two drugs in the regimen, *ca*pecitabine and *gem*citabine.

INDICATION(S)

The CapGem regimen (see Table 1) has been studied as neoadjuvant therapy of locally advanced pancreatic cancer,¹ post radiotherapy of bile duct cancer,² initial therapy for advanced or metastatic biliary,³⁻⁷ cholangiocarcinoma and gallbladder,^{8,9} and pancreatic cancer.^{7,10-20} Current guidelines list CapGem as an acceptable regimen for locally advanced unresectable or metastatic pancreatic cancer in patients with good performance status.²¹

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when dispensing capecitabine and preparing gemcitabine.

A. Capecitabine

1. Capecitabine is available as 500 mg and 150 mg tablets.
2. Capecitabine tablets are unscored and film-coated; breaking or cutting the tablets is difficult and not recommended.

B. Gemcitabine

1. Use gemcitabine injection 38 mg/mL or powder for injection.

2. Reconstitute the lyophilized powder to a concentration of 38 mg/mL.
 - a. When reconstituted according to the manufacturer's recommendation, the final concentration is 38 mg/mL, *not* 40 mg/mL.
 - b. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided.
3. Dilute with 50 to 250 mL 0.9% sodium chloride injection for infusion.

DRUG ADMINISTRATION

A. Capecitabine

1. Capecitabine is administered orally in 2 divided doses daily.
2. Tablets should be swallowed with water within 30 minutes after a meal.
3. The dose is often prescribed as the *total daily dose*, which is *twice the individual dose* (eg, 2,000 mg/m²/day = 1,000 mg/m² twice a day).
4. Care should be taken to ensure the intended daily dose is not taken twice a day.

B. Gemcitabine

1. Gemcitabine is given as a short (30 minute) intravenous (IV) infusion.
2. Two of the CapGem studies reviewed used a fixed-dose rate (FDR) of 10 mg/m²/min.^{1,7}
3. Infusion times greater than 60 minutes have been associated with increased grade 3 or 4

Table 1. GemCAP regimen^{3-6,9,12,14,15,20}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Gemcitabine	1,000 mg/m ²	IV	1, 8	2,000 mg/m ²
Capecitabine	1,300 mg/m ² (650 mg/m ² twice daily)	PO	1 through 14	18,200 mg/m ²
<i>Cycle repeats: every 3 weeks</i>				
Variations				
1.	Gemcitabine 1,250 mg/m ² IV days 1 and 8, capecitabine 950 mg/m ² PO twice daily days 1 through 14 every 3 weeks. ¹			
2.	Gemcitabine 1,000 mg/m ² IV days 1 and 8, capecitabine 750 mg/m ² PO twice daily days 1 through 14 every 3 weeks. ²			
3.	Gemcitabine 1,250 mg/m ² IV days 1 and 8, capecitabine: 800 mg/m ² PO twice daily days 1 through 14 1,000 mg/m ² PO twice daily days 1 through 14 1,250 mg/m ² PO twice daily days 1 through 14 1,500 mg/m ² PO twice daily days 1 through 14 every 3 weeks. ⁷			
4.	Gemcitabine 1,000 mg/m ² IV days 1 and 8, capecitabine 1,000 mg/m ² PO twice daily days 1 through 14 every 3 weeks. ^{8,13}			
5.	Gemcitabine 2,200 mg/m ² IV day 1, capecitabine 2,500 mg/m ² PO daily days 1 through 7 every 14 days. ¹⁰			
6.	Gemcitabine 1000 mg/m ² IV days 1 and 8, capecitabine: 500 mg/m ² PO twice daily days 1 through 14 650 mg/m ² PO twice daily days 1 through 14 800 mg/m ² PO twice daily days 1 through 14 every 3 weeks. ¹¹			
7.	Gemcitabine 1,000 mg/m ² IV days 1, 8, and 15, capecitabine 830 mg/m ² PO twice daily days 1 through 21 every 4 weeks. ^{16,19}			
8.	Gemcitabine 1,000 mg/m ² IV days 1 and 8, capecitabine 825 mg/m ² PO twice daily days 1 through 14 every 3 weeks. ¹⁷			
9.	Gemcitabine: 20 mg/m ² IV Monday and Thursday 20 mg/m ² IV Monday and Thursday 30 mg/m ² IV Monday and Thursday every week during radiation therapy. ¹⁸	Capecitabine: 80 mg/m ² PO twice daily Monday through Friday 1,000 mg/m ² PO twice daily days 1 through 14 1,300 mg/m ² PO twice daily days 1 through 14		

Note: IV = intravenous; PO = oral.

hematologic toxicity caused by accumulation of the active metabolite gemcitabine triphosphate.²²

SUPPORTIVE CARE

A. Acute Emesis Prophylaxis: The CapGem regimen is predicted to cause acute emesis in 10% to 30% of patients.²³⁻²⁶ The studies reviewed reported nausea in 21% to 55% of patients,^{6,20} with grade 3 or 4 nausea in 2% to 7% of patients.^{4,6,14,20} Vomiting was reported in 34% of patients,⁶ with grade 3 or 4 vomiting reported in 2% to 4% of patients.^{4,6,14} Prophylactic antiemetic therapy with a serotonin antagonist is recommended,²⁴⁻²⁶ but may not be required in all patients. One group suggests addition of a neurokinin (NK₁) antago-

nist may be appropriate in some patients.²⁴ One of the following regimens given 30 minutes prior to therapy is recommended:

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

Prophylactic use of a NK₁ antagonist is recommended for moderately emetogenic regimens

if the 2-drug combination was not effective in the previous treatment cycle.²⁴⁻²⁶ One of the following regimens is recommended:

1. Ondansetron 8 mg to 16 mg, dexamethasone 12 mg, and aprepitant 125 mg given PO 30 minutes before CapGem.
2. Granisetron 1 mg to 2 mg, dexamethasone 12 mg, and aprepitant 125 mg given PO 30 minutes before CapGem.
3. Dolasetron 100 mg, dexamethasone 12 mg PO, and aprepitant 125 mg given PO 30 minutes before CapGem.
4. Palonosetron 0.25 mg IV, dexamethasone 12 mg, and aprepitant 125 mg given PO 30 minutes before CapGem on day 1 only.

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.²⁷ 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 CapGem.
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 CapGem.
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 CapGem.

If a NK₁ 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 CapGem.
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 CapGem.

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 CapGem.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.²³⁻²⁶ 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.²⁸⁻³²

- B. Breakthrough Nausea and Vomiting²³⁻²⁶:** 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.

Patients who do experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.²³⁻²⁶ 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.²⁸⁻³²

- 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 (CSF) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSF should be considered. For regimens with an incidence of febrile neutropenia

less than 10%, routine prophylactic use of CSF is not recommended.^{33,34} Since febrile neutropenia was reported in only 1% to 7% of patients in the studies reviewed,^{3,4,14} prophylactic use of CSF is not recommended.^{32,33} CSF may be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of CapGem.

D. Diarrhea: Diarrhea is a frequent consequence of capecitabine administration. 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 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 after each unformed stool, or as often as every 2 hours for 24 hours.³⁵ Patients should be counseled to³⁶:

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).

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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). 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: Ascites (grade 3) 8%,⁹ dehydration (grade 3) 8%,⁹ lower extremity deep venous thrombosis (grade 4) 8%,⁹ pleural effusion (grade 3) 8%,⁹ pulmonary embolism (grade 4) 8%,⁹ thromboembolic events (grade 4) (grade 2) 2%.³

B. Central Nervous System: Insomnia (grade 2) 2%.⁴

C. Constitutional: Fatigue 73%,⁶ (grade 2) 42%,³ (grade 3) 4% to 8%,^{3,9} (grade 3 or 4) 11%⁶; fever (grade 2) 2%³; weakness (grade 2) 3%.⁴

D. Dermatologic: Hand-foot rash (grade 2) 20%,³ (grade 3) 9%³; skin rash 16%,²⁰ (grade 2) 2%.³

E. Endocrine/metabolic: Hyperglycemia (grade 3) 17%,⁹ hyperkalemia (grade 3) 8%.⁹

F. Gastrointestinal: Anorexia 59%,⁶ (grade 2) 3%,⁴ (grade 3) 2%,⁴ (grade 3 or 4) 7%⁶; constipation (grade 2) 5%,⁴ (grade 3) 2%,^{4,12} (grade 4) 8%⁹; diarrhea 23%,⁶ (grade 2) 2%,³ (grade 3) 2% to 8%,^{9,12} (grade 3 or 4) 2% to 5%^{6,14}; mucositis/stomatitis 9%,⁶ (grade 2) 9%³; nausea 21% to 55%,^{6,20} (grade 2) 7% to 12%,^{3,4} (grade 3) 2%,⁴ (grade 3 or 4) 5% to 7%^{6,14,20}; vomiting 34%,⁶ (grade 2) 2% to 8%,^{3,4} (grade 3) 3%,⁴ (grade 3 or 4) 2% to 4%.^{6,14}

G. Hematologic: Anemia 53% to 93%,^{6,20} (grade 3) 8% to 9%,^{9,12} (grade 3 or 4) 2% to 8%^{6,14,20}; epistaxis (grade 3) 8%,⁹ febrile neutropenia (grade 3) 2% to 7%,^{3,4} (grade 3 or 4) 1%¹⁴; gastrointestinal bleeding (grade 3) 1%⁵; increased prothrombin time (grade 3) 8%,⁹ leukopenia 82%,⁶ (grade 3 or 4) 11%⁶; neutropenia 74%,²⁰ (grade 2) 33%,³ (grade 3) 1% to 32%,^{3-5,9,12} (grade 3 or 4) 23% to 37%,^{14,20} (grade 4) 2% to 9%^{3,12}; thrombocytopenia 32% to 70%,^{6,20} (grade 2) 9%,³ (grade 3) 1% to 9%,^{4,5,12} (grade 3 or 4) 4% to 11%,^{6,14,20} (grade 4) 4% to 8%.^{9,12}

H. Hepatic: Elevated bilirubin 17%⁹; elevated alanine aminotransferase (ALT) (grade 3) 8%⁹; elevated aspartate aminotransferase (AST) (grade 3) 8%.⁹

I. Infection: (grade 2) 7%,³ (grade 3) 4% to 8%.^{3,9}

J. Neurologic: Asthenia (grade 3) 2%¹²; hand-foot syndrome 11% to 32%,^{5,20} (grade 2) 9%,⁴ (grade 3 or 4) 5%.²⁰

K. Pulmonary: Dyspnea (grade 3) 8%,⁹ (grade 4) 8%.⁹

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. AST/ALT
2. Total bilirubin
3. Serum creatinine

4. Complete blood count (CBC) with differential

B. Prior to each treatment

1. AST/ALT
2. Total bilirubin
3. CBC with differential

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

1. White blood cell count (WBC):
 - a. Greater than or equal to 3,000 cells/mcL.⁹
 - b. Greater than or equal to 3,500 cells/mcL.¹⁴
2. Absolute neutrophil count (ANC):
 - a. Greater than or equal to 1,500 cells/mcL.^{3,5,6,9,12}
3. Platelet count:
 - a. Greater than or equal to 100,000 cells/mcL.^{3,5,6,9,14}
 - b. Greater than or equal to 120,000 cells/mcL.¹²
4. Hemoglobin:
 - a. Greater than or equal to 10 g/dL.¹⁴
5. Serum creatinine:
 - a. Less than or equal to 1.8 mg/dL.^{3,5}
 - b. Less than or equal to 1.6 mg/dL.⁹
 - c. Less than or equal to 1.2 mg/dL.¹²
6. Creatinine clearance:
 - a. Greater than or equal to 60 mL/min.^{3,5}
 - b. Greater than or equal to 50 mL/min.⁶
 - c. Greater than or equal to 30 mL/min.¹⁴
7. Serum bilirubin:
 - a. Less than or equal to 3 times the upper limit of normal (ULN) and stable for 2 weeks.³
 - b. Less than or equal to 3 times the ULN.^{4,5}
 - c. Less than or equal to 4 times the ULN.⁶
 - d. Less than or equal to 5 times the ULN.¹⁴
 - e. Less than 3 mg/dL.^{9,12}
8. ALT:
 - a. Less than or equal to 5 times the ULN and stable for 2 weeks.³
 - b. Less than or equal to 5 times the ULN.^{4-6,14}
 - c. Within normal limits.¹²
9. AST:
 - a. Within normal limits.¹²
 - b. Less than or equal to 5 times the ULN.¹⁴

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. Capecitabine – Creatinine clearance:
 - a. Less than or equal to 50 mL/min and greater than or equal to 30 mL/min, reduce dose 25%.³⁷
 - b. Less than 30 mL/min, do not give drug.³⁷
2. Gemcitabine
 - a. No adjustment necessary.^{37,38}
 - b. Creatinine
 - (1) Greater than 3 mg/dL, do not give the drug.⁹
 - (2) Greater than 2 mg/dL and less than or equal to 3 mg/dL, and creatinine clearance⁹:
 - (a) Greater than or equal to 10 mL/min, reduce dose to 800 mg/m².
 - (b) Less than 10 mL/min, do not give the drug.

B. Liver Function

1. Capecitabine – no adjustment necessary.³²
2. Gemcitabine – no adjustment necessary.^{37,39}

C. Myelosuppression

1. Gemcitabine
 - a. Reduce dose 25% for:
 - (1) Febrile neutropenia.³
 - (2) Febrile neutropenia or grade 3 or 4 neutropenia with prophylactic growth factor.⁴
 - (3) Grade 4 hematologic toxicity lasting more than 7 days.³
 - (4) Grade 3 or 4 hematologic toxicity.⁶
 - (5) Bleeding associated with thrombocytopenia.³
 - (6) ANC 500 to 999 cells/mcL or platelets 50,000 to 99,999 cells/mcL.⁹
 - (7) ANC 500 to 1000 cells/mcL or platelets 50,000 to 100,000 cells/mcL on day 8.³
 - b. ANC less than 500 cells/mcL or platelets less than 50,000 cells/mcL, do not give gemcitabine.⁶
2. Capecitabine
 - a. Any grade 4 hematologic toxicity, do not give drug.³
 - b. Febrile neutropenia or grade 3 or 4 neutropenia with prophylactic growth factor, reduce dose 25%.¹²
3. Afebrile neutropenia grade 3 or 4, add prophylactic growth factor.^{4,12}

4. Thrombocytopenia (grade 3 or 4) lasting more than 5 days, reduce the dose of both drugs 25%.^{4,12}

D. Nonhematologic Toxicity

1. Gemcitabine
 - a. Greater than or equal to grade 3 toxicity, reduce dose 25%.³
 - b. Grade 3 toxicity, reduce dose 25%.⁶
 - c. Grade 4 toxicity, reduce dose 50%.⁶
2. Capecitabine
 - a. Greater than or equal to grade 3 toxicity, reduce dose 25%.³
 - b. Grade 3 toxicity, reduce dose 25%.^{6,20}
 - c. Grade 4 toxicity, reduce dose 50%.⁶
 - d. Diarrhea (grade 3 or 4), reduce dose 25%.^{4,12}
 - e. Hand-foot syndrome (grade 3 or 4), reduce dose 25%.^{4,12}

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