Cancer Chemotherapy Update

Gemcitabine and Vinorelbine (GemVin) Regimen

Elizabeth Y. Shang, PhD, RPh^{}; 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: Gemcitabine and vinorelbine (GemVin)

Origin of Name: The regimen is named for the 2 drugs it contains: gemcitabine and vinorelbine.

INDICATION(S)

The gemcitabine and vinorelbine (GemVin) regimen has been studied as first-line treatment for advanced small cell¹ and non-small cell lung cancer (NSCLC),^{2–22} first-line or salvage treatment for metastatic breast cancer,^{23–36} salvage treatment for advanced Hodgkin and non-Hodgkin's lymphomas,^{37–40} and first-line therapy for advanced adenocarcinoma of unknown primary (CUP).⁴¹ Summary of the regimen is provided in Table 1. Current guidelines recommend it as a first-line therapy for advanced NSCLC.⁴² It is not listed as a recommended regimen for small cell lung cancer, breast cancer, CUP, or Hodgkin and non-Hodgkin's lymphomas.^{42–47}

DRUG PREPARATION

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

A. Gemcitabine

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

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

B. Vinorelbine

1. Use vinorelbine injection 10 mg/mL.
2. For syringes, dilute the dose to a final volume of 30 mL with NS or 5% dextrose injection (D5W).
3. For infusion, dilute the dose in 50 to 250 mL NS, D5W, or a saline/dextrose solution.

DRUG ADMINISTRATION

A. Gemcitabine

1. In the studies reviewed, the drug was given as a 30-minute intravenous (IV) infusion.
2. Infusion times greater than 60 minutes have been associated with increased grade 3 or 4 hematologic toxicity caused by accumulation of the active metabolite gemcitabine triphosphate.⁴⁸

- B. Vinorelbine** is administered as slow IV push over 6 to 10 minutes, or as a short (10 to 30 minutes) infusion.

^{**}Dr. Shang is a pharmacist with the American Red Cross, Department of Pharmacy, Walter Reed National Military Medical Center, Bethesda, Maryland.

Table 1. Gemcitabine and vinorelbine ^{1–9,23–25,28,37,41}

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
Vinorelbine	25 mg/m ²	IV	1,8	50 mg/m ²
<i>Cycle repeats: every 3 weeks</i>				
Variations				
1.	Gemcitabine 1,000 mg/m ² and vinorelbine 30 mg/m ² given on days 1 and 8 every 3 weeks was used in a number of trials. ^{9,31,39,40}			
2.	Suyani et al used gemcitabine 1,000 mg/m ² and vinorelbine 30 mg/m ² on days 1, 8, and 15 every 4 weeks. ³⁸			
3.	Greco et al used gemcitabine 1,000 mg/m ² and vinorelbine 25 mg/m ² on days 1, 8, and 15 every 4 weeks. ^{16,17}			
4.	Haider et al used gemcitabine 1,000 mg/m ² on days 1, 15, and 21 and vinorelbine 30 mg/m ² on days 1 and 21 every 5 weeks. ³³			
5.	Gemcitabine 1,200 mg/m ² and vinorelbine 30 mg/m ² given on days 1 and 8 every 3 weeks was used in a number of trials. ^{14,15,26,27,29,30}			
6.	Valenza et al used gemcitabine 1,000 mg/m ² on days 1, 15, and 21 and vinorelbine 25 mg/m ² on days 1 and 8 every 3 weeks. ³²			
7.	Gemcitabine 1,000 mg/m ² and vinorelbine 25 mg/m ² given on day 1 every 2 weeks was used in 2 trials. ^{18,34}			
8.	Pallis et al used gemcitabine 1,000 mg/m ² and vinorelbine 25 mg/m ² on days 1 and 15 every 4 weeks. ³⁵			
9.	Morabito et al used gemcitabine 800 mg/m ² and vinorelbine 25 mg/m ² on days 1 and 8 every 3 weeks. ³⁶			
10.	Esteban et al used gemcitabine 1,250 mg/m ² and vinorelbine 30 mg/m ² on days 1 and 8 every 3 weeks. ¹²			
11.	Boni et al used gemcitabine 1,250 mg/m ² and vinorelbine 25 mg/m ² on days 1 and 8 every 3 weeks. ¹³			
12.	Gridelli et al used gemcitabine 1,200 mg/m ² and vinorelbine 25 mg/m ² on days 1 and 8 every 3 weeks. ⁹			
13.	Han et al used gemcitabine 900 mg/m ² and vinorelbine 25 mg/m ² on days 1 and 8 every 3 weeks. ¹⁹			
14.	Chen et al used gemcitabine 800 mg/m ² and vinorelbine 20 mg/m ² on days 1, 8, and 15 every 4 weeks. ^{20,21}			
15.	Flotten et al used gemcitabine 1,000 mg/m ² and vinorelbine 60 mg/m ² PO on days 1 and 8 every 3 weeks. ²²			

Note: IV = intravenous; PO = oral.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The Gem-Vin regimen is predicted to cause acute emesis in 10% to 30% of patients.^{49–52} The studies reviewed reported mild (grade 1 or 2) nausea or vomiting in 2% to 31% of patients,^{1,2,4,5,10,11,23,25,28} and moderate to severe (grade 3 or 4) nausea or vomiting in 0.4% to 24% of patients.^{2,3,5,6,8,23–25,41} For most patients, prophylactic antiemetic therapy with a single agent is recommended. One of the following regimens is recommended:

1. Dexamethasone 8 mg to 12 mg orally (PO), given 30 minutes before GemVin.
2. Prochlorperazine 10 mg PO, ±diphenhydramine 25 to 50 mg PO if needed, given 30 minutes before GemVin.

3. Metoclopramide 0.5 to 2 mg/kg PO, ±diphenhydramine 25 to 50 mg PO if needed, given 30 minutes before GemVin.
4. Promethazine 25 to 50 mg PO, ±diphenhydramine 25 to 50 mg PO if needed, given 30 minutes before GemVin.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category added to the previous prophylactic antiemetic regimen.^{49–52} The following regimens are recommended:

1. Patients who received a steroid only, add a dopamine antagonist.
2. Patients who received a dopamine antagonist only, add a steroid.

3. Patients who received a steroid and dopamine antagonist, substitute a serotonin antagonist for the dopamine antagonist.

If a steroid and dopamine antagonist combination is not effective, a serotonin antagonist and steroid combination may be required. The following regimens are recommended:

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

Patients who do not respond to a 2-drug combination may benefit from a steroid, dopamine antagonist, and serotonin antagonist regimen or the addition of a neurokinin (NK₁) antagonist to their previous regimen.

- B. Breakthrough Nausea and Vomiting^{49–52}:** Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is suggested:

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.

A few small studies suggest that higher doses of granisetron (3 mg IV or 40 mcg/kg to 240 mcg/kg)^{53–57} may be effective in treating breakthrough nausea, however none of these reports found the improvement to be statistically significant.

- 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.^{58,59} Because febrile neutropenia was reported in 1% to 14% of patients in the trials of gemcitabine and vinorelbine reviewed,^{3–5,8,9,25} prophylactic use of CSF is not recommended. Some patients with risk factors such as age, poor performance status, extensive previous myelosuppressive therapy, or renal or hepatic dysfunction may benefit from prophylactic use of CSF. CSF should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of GemVin.

- D. Extravasation:** Vinorelbine is a moderate vesicant; extravasation should be avoided. If extravasation occurs, stop the infusion immediately and aspirate as much of the extravasated solution as possible before withdrawing the needle. The limb should be elevated and cooled intermittently (ice packs for 15–20 minutes 4 times a day for 3 days).^{60,61} Although Larson reported applying ice to all extravasations,^{60,61} most other groups suggest dry heat for 30 minutes 4 times a day for 3 days.⁶² Hyaluronidase 150 units/mL injected intradermally at the extravasation site also has been recommended for treatment of vinca alkaloid extravasations.⁶²

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. Two frequently used systems are 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) and the World Health Organization (WHO) Criteria.⁶³ 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:** Arrhythmias (grade 1) 2%,¹¹ (grade 2) 3%,¹¹ (grade 3) 4%,¹¹ (grade 4) 2% to 3%^{1,11}; edema (grade 1) 5%,¹⁰ (grade 2) 10%,²⁸ (grade 3) 10%²⁸; phlebitis (grade 1) 9%,¹¹ (grade

- 2) 5% to 29%,^{4,11,28} (grade 1 or 2) 17%,³⁷ (grade 3) 1%,¹¹ (grade 3 or 4) 3%³⁷; unspecified cardiac toxicity (grade 1) 0.4% to 2%,^{5,6} (grade 2) 0.4% to 3%,^{1,5,6} (grade 3) 0.4% to 8%,^{5,6} (grade 4) 1% to 3%^{1,6}; vasculitis (grade 1) 4%²; venous irritation (grade 3 or 4) 3%.⁸
- B. Central Nervous System:** Unspecified toxicity (grade 1) 0.8% to 7%.^{5,6,9}
- C. Dermatologic:** Alopecia (grade 1) 5% to 36%,^{1,2,6,10,11,23} (grade 1 or 2) 24%,²⁵ (grade 2) 1% to 12%,^{2,5,6,9,11,23} (grade 3) 0.4% to 2%,^{5,6,11,41} (grade 1 to 4) 6%⁷; rash (grade 2) 18%,⁴ (grade 3) 2%⁴; skin rupture (grade 2) 6%,² (grade 3) 2%²; unspecified skin unspecified toxicity (grade 1) 2% to 3%,^{1,6} (grade 2) 0.4% to 7%.^{1,6,9}
- D. Gastrointestinal:** Anorexia (grade 1) 13% to 27%,^{1,28} (grade 1 to 2) 1%,²⁵ (grade 2) 10% to 24%,^{1,28} (grade 3) 2% to 16%,^{28,41} (grade 3 or 4) 4%⁸; constipation (grade 1) 2% to 20%,^{1,6,11,28} (grade 2) 3% to 31%,^{1,4-6,9,11,28} (grade 3) 1% to 3%,^{1,4-6,11} (grade 3 or 4) 2%,⁸ (grade 1 to 4) 17%⁷; diarrhea (grade 1) 3% to 10%,^{1,2,6,11,23} (grade 1 or 2) 22%,²⁵ (grade 2) 1% to 6%,^{1,2,4-6,11,23} (grade 3) 2%,^{3-5,9} (grade 3 or 4) 11%,²⁵ (grade 4) 1%,¹¹ (grade 1 to 4) 5%⁷; mucositis (grade 1) 3%,^{6,11} (grade 2) 1% to 2%,^{5,6,11} (grade 3) 0.4% to 5%,^{6,9,11} (grade 4) 1%¹¹; nausea and vomiting (grade 1) 15% to 31%,^{10,11,23,28} (grade 2) 13% to 28%,^{11,23} (grade 1 or 2) 17%,³⁷ (grade 3) 6%,²³ (grade 3 or 4) 2%,⁸ (grade 1 to 4) 33%⁷; nausea (grade 1) 10% to 16%,^{1,2} (grade 1 or 2) 24%,²⁵ (grade 2) 13 to 21%,^{1,2,4} (grade 3) 2% to 11%,^{2,3,41} (grade 3 or 4) 3% to 5%^{24,25}; vomiting (grade 1) 2% to 14%,^{1,2,6} (grade 1 or 2) 16%,²⁵ (grade 2) 5% to 10%,^{1,2,4,6} (grade 3) 0.4% to 4%,^{5,6} (grade 3 or 4) 2% to 24%,^{24,25} (grade 4) 2%⁴¹; stomatitis (grade 1) 13% to 17%,^{1,23} (grade 1 or 2) 11%,²⁵ (grade 2) 12%,²³ (grade 3 or 4) 11%.²⁵
- E. Hematologic:** Anemia (grade 1) 9% to 60%,^{1,2,6,11,23,28} (grade 1 or 2) 40% to 53%,^{10,25} (grade 2) 2% to 61%,^{1,2,5,6,11,23,28} (grade 3) 2% to 26%,^{1-4,6,11,28} (grade 3 or 4) 1% to 5%,^{8,24,25} (grade 4) 0.4% to 5%^{2,3,6}; bleeding (grade 1) 1%,⁶ (grade 2) 0.4% to 2%^{5,6}; febrile neutropenia (grade 2) 14%,⁹ (grade 3) 14%,³ (grade 3 or 4) 1% to 14%,^{4,8,25} (grade 4) 4%⁵; leukopenia (grade 1) 6% to 29%,^{2,6,23,28} (grade 1 or 2) 32%,²⁵ (grade 2) 7% to 51%,^{2,6,23,28} (grade 3) 2% to 42%,^{2-6,9,23,28} (grade 3 or 4) 5% to 8%,^{8,25} (grade 4) 2% to 16%^{2-4,6,9,23,28}; neutropenia (grade 1) 5% to 16%,^{1,2,6,11} (grade 1 or 2) 15% to 39%,^{10,25} (grade 3) 3% to 65%,^{1-6,9,11,41} (grade 3 or 4) 10% to 23%,^{7,8,10,24,25} (grade 4) 2% to 35%^{1-6,9,11,41}; thrombocytopenia (grade 1) 3% to 48%,^{1,2,6,11,23,28} (grade 1 or 2) 5%,^{10,25} (grade 2) 2% to 20%,^{1,2,6,11,28} (grade 3) 2% to 12%,^{1-6,11,28,41} (grade 3 or 4) 1% to 5%,^{7,8,24,25} (grade 4) 0.4% to 7%.^{5,6,9,11,41}
- F. Hepatic:** Alkaline phosphatase elevation (grade 1) 51%,²⁸ (grade 2) 12%,²⁸ (grade 3) 2%²⁴; AST or ALT elevation (grade 1) 15% to 36%,^{2,11} (grade 2) 7% to 44%,^{2,4,11} (grade 3) 2% to 19%,^{2-4,11,28} (grade 4) 1% to 2%^{3,11}; liver failure 1%²⁵; unspecified hepatic toxicity (grade 1) 3% to 6%,^{1,6,23} (grade 2) 2% to 7%,^{1,5,6,9} (grade 3) 3%,¹ (grade 4) 2%.⁹
- G. Infection:** Septic shock 1%²⁵; (grade 1) 1% to 12%,^{2,6,28} (grade 1 or 2) 9%,³⁷ (grade 2) 2% to 8%,^{2,5,6} (grade 3) 0.4% to 21%,^{2,3,6,28} (grade 3 or 4) 1% to 6%,^{8,25,37} (grade 4) 2% to 3%.^{3,5,28}
- H. Hypersensitivity:** Allergy (grade 1) 1%⁶; injection reaction (grade 1 or 2) 15%,²⁵ (grade 3 or 4) 14%;²⁵ rash (grade 1 or 2) 7%.³⁷
- I. Metabolic:** Fatigue (grade 1) 7% to 23%,^{1,6,28} (grade 2) 8% to 41%,^{1,4,6,28} (grade 1 or 2) 21%,³⁷ (grade 3) 2% to 8%,^{1,4-6,9,28} (grade 4) 2%⁵; fever (grade 1) 5% to 34%,^{2,6,10} (grade 1 or 2) 6% to 7%,^{25,37} (grade 2) 3% to 13%,^{1,2,6,23} (grade 3) 1% to 2%^{6,23}; hyperglycemia (grade 1) 51%,²⁸ (grade 2) 15%,²⁸ (grade 3) 15%²⁸; weight loss (grade 1) 3%.¹
- J. Neurologic:** Asthenia (grade 1) 7% to 12%,^{23,28} (grade 1 or 2) 15%,²⁵ (grade 2) 20% to 29%,^{23,28} (grade 3) 2%,²⁸ (grade 3 or 4) 4%⁸; motor neuropathy (grade 1) 2% to 3%,^{1,28} (grade 2) 2%,¹¹ (grade 3) 2% to 5%^{11,28}; neuropathy (grade 1) 6%⁵; otic (grade 1) 0.8% to 2%,^{6,11} (grade 2) 2%¹¹; peripheral neuropathy (grade 1) 4%,⁶ (grade 2) 1%,⁶ (grade 1 to 4) 5%⁷; sensory neuropathy/neurotoxicity (grade 1) 4% to 29%,^{1,11,23,28} (grade 2) 3% to 22%,^{1,11,23,28} (grade 3) 1% to 5%^{11,28}; unspecified neurologic toxicity (grade 1) 4%,² (grade 3) 2% to 4%,^{9,41} (grade 4) 2%.⁴¹
- K. Pulmonary:** Dyspnea (grade 1) 10% to 15%,^{2,28} (grade 2) 12%,^{2,28} (grade 3) 7%,²⁸ (grade 3 or 4) 2%²⁴; pneumonitis (grade 2) 5%,⁴ (grade 3) 2% to 5%,^{3,4} (grade 4) 2%,³ (grade 5) 2%⁴; unspecified pulmonary toxicity (grade 1) 2% to 5%,^{6,10} (grade 2) 1% to 2%,^{6,9} (grade 3) 0.4% to 2%.^{5,6}

- L. Renal:** Creatinine elevation (grade 1) 4%,^{2,11} (grade 2) 1% to 2%,^{4,11} (grade 3) 2%,⁴; unspecified renal toxicity (grade 1) 1%.⁶
- M. Skeletal/Muscle:** Bone pain (grade 2) 2%,⁹ (grade 1 or 2) 13%,³⁷ (grade 3 or 4) 2%,²⁴ (grade 4) 2%; myalgia (grade 1) 20%,²⁸ (grade 2) 44%.²⁸
- N. Other:** Itching (grade 3) 3%.¹

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. AST/ALT
2. Total bilirubin
3. Serum creatinine
4. 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. White blood cell count (WBC):
 - a. Greater than or equal to 3,000 cells/mcL.²⁴
 - b. Greater than or equal to 3,500 cells/mcL.^{4,23}
 - c. Greater than or equal to 4,000 and less than or equal to 12,000 cells/mcL.²
2. Absolute neutrophil count:
 - a. Greater than 1,000 cells/mcL.⁴¹
 - b. Greater than 1,500 cells/mcL¹⁰ or greater than or equal to 1,500 cells/mcL.³
 - c. Greater than or equal to 2,000 cells/mcL.^{1,4-6,11,23,24}
 - d. Greater than or equal to 3,000 cells/mcL.²⁸
3. Platelet count: greater than 100,000 cells/mcL^{5,10} or greater than or equal to 100,000 cells/mcL.^{1-4,6,11,23,24,28,41}
4. Hemoglobin:
 - a. Greater than or equal to 8 mg/dL.²⁴
 - b. Greater than or equal to 9 mg/dL.²³
 - c. Greater than 9.5 mg/dL.²
 - d. Greater than 10 mg/dL¹⁰ or greater than or equal to 10 mg/dL.^{1,4-6}
5. Serum creatinine:
 - a. Less than or equal to 1.2 mg/dL.⁴
 - b. Less than 1.5 mg/dL² or less than or equal to 1.5 mg/dL.²⁸
 - c. Less than or equal to 2 mg/dL.²³
 - d. Less than or equal to 1.5 mg/dL and serum creatinine clearance greater than or equal to 60 mL/min.³
 - e. Less than or equal to 1.25 times the upper limit of normal (ULN).⁶

- f. Less than or equal to 1.5 times ULN.^{1,11}
- g. Less than or equal to 2 times ULN.⁴¹
- h. Serum creatinine clearance greater than or equal to 60 mL/min.²⁴

6. Serum bilirubin

- a. Less than 1.5 mg/dL^{10,23} or less than or equal to 1.5 mg/dL.^{3,4,11}
- b. Less than or equal to 1.25 times ULN.^{5,6}
- c. Less than or equal to 1.5 times ULN.^{1,2}
- d. Less than or equal to 2 times ULN.⁴¹

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

DOSAGE MODIFICATIONS

A. Renal Function

1. Gemcitabine: No adjustment is required.^{64,65}
2. Vinorelbine: No adjustment is required.⁶⁶

B. Liver Function

1. Gemcitabine:
 - a. No adjustment is required.⁶⁷
 - b. If bilirubin is greater than 1.6 mg/dL, start the dose at 800 mg/m².⁶⁸
 - c. If bilirubin is greater than or equal to 1.5 times ULN **or** ALT/AST is greater than or equal to 5 times the ULN, reduce dose by 25%.³
2. Vinorelbine:
 - a. If the bilirubin is greater than or equal to 2 mg/dL and less than or equal to 3 mg/dL, reduce the dose by 50%.⁶⁶
 - b. If the bilirubin is greater than or equal to 2.1 mg/dL and less than or equal to 3 mg/dL, reduce the dose by 50%.⁶⁸
 - c. If the bilirubin is greater than or equal to 3.1 mg/dL and less than or equal to 5 mg/dL, reduce the dose by 75%.⁶⁶
 - d. If the bilirubin is greater than 3 mg/dL, reduce the dose by 75%.⁶⁸
 - e. If the bilirubin is greater than 5 mg/dL, do not give the drug.⁶⁶
 - f. If bilirubin is greater than or equal to 1.5 times ULN, reduce dose by 25%.³
 - g. If AST/ALT is greater than or equal to 5 times ULN, reduce dose by 25%.³

C. Myelosuppression

1. Neutropenia
 - a. Less than 2,000 cells/mcL, omit dose.⁶
 - b. Less than or equal to 1,500 cells/mcL: If on day 1, postpone treatment up to 2 weeks. If on day 8, omit the dose.⁵

- c. Greater than or equal to 500 and less than or equal to 1,000 cells/mcL, reduce dose by 25%.²⁸
- d. Less than 500 cells/mcL, hold the dose until counts recover.²⁸
- e. Febrile neutropenia:
 - (1) Reduce dose by 25%.³
 - (2) Reduce dose by 20%.²
- f. Grade 2 neutropenia, delay day 1 dose.⁸
- g. Grade 3 neutropenia, omit day 8 dose.⁸
- h. Grade 4 neutropenia lasted for 4 days, reduce dose by 20%.²
- i. Grade 4 neutropenia, reduce dose by 20%.⁴
- 2. Leucopenia
 - a. Less than or equal to 2,500 cells/mcL, postpone treatment by 1 week.⁴¹
 - b. Greater than or equal to 2,000 and less than or equal to 2,500 cells/mcL, reduce dose by 25%.²⁴
 - c. Less than 2,000 cells/mcL, omit the dose.²⁴
 - d. Greater than or equal to 1,000 and less than or equal to 1,500 cells/mcL, reduce dose by 25%.¹⁰
 - e. Greater than or equal to 1,00 and less than or equal to 1,500 cells/mcL and platelets counts greater than or equal to 75,000 and less than or equal to 100,000 cells/mcL, reduce dose by 50%.¹⁰
 - f. Less than 1,000 cells/mcL, omit the dose.¹⁰
 - g. Greater than or equal to grade 3, reduce dose by 25%.⁴¹
- 3. Thrombocytopenia
 - a. Less than 100,000 cells/mcL, omit dose.⁶
 - b. Less than or equal to 100,000 cells/mcL, on day 8 do not give the drugs.⁵
 - c. Greater than or equal to 50,000 and less than or equal to 75,000 cells/mcL, reduce dose of gemcitabine and vinorelbine by 25%.²⁸
 - d. Less than 75,000 cells/mcL, omit the dose.¹⁰
 - e. Less than 50,000 cells/mcL, hold the dose until counts recover.²⁸
 - f. Less than 25,000 or thrombocytopenia with transfusion, reduce dose of gemcitabine and vinorelbine by 25%.³
 - g. Less than or equal to 20,000 cells/mcL, reduce dose of gemcitabine and vinorelbine by 20%.²⁴
 - h. Grade 1 thrombocytopenia, delay day 1 dose.⁸
 - i. Grade 2 thrombocytopenia, postpone treatment by 1 week.⁴¹
 - j. Grade 3 thrombocytopenia, omit day 8 dose.⁸
 - k. Greater than or equal to grade 3 leucopenia, reduce dose by 25%.⁴¹
- D. Neurotoxicity**
 - 1. Grade 2 or 3, reduce dose of vinorelbine by 20% or 30%.³
 - 2. Greater than or equal to grade 2, delay administration of vinorelbine by 1 week.¹⁰
 - 3. Greater than or equal to grade 2, reduce dose of gemcitabine and vinorelbine by 25% or delay treatment.⁴¹
- E. Nonhematologic toxicities**
 - 1. Greater than or equal to grade 2 except alopecia, omit doses.^{6,10}
 - 2. Greater than or equal to grade 3 except nausea, vomiting, or alopecia, reduce dose by 20%.²
 - 3. Greater than or equal to grade 3, reduce dose by 20%.⁴
 - 4. Grade 3 toxicities except nausea or vomiting, reduce dose by 50%.²⁴
 - 5. Nausea, vomiting, or mucositis greater than or equal to grade 3, reduce dose by 20%.³
 - 6. Greater than or equal to grade 3, reduce dose by 50%.³

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