DRUG NAME: Gemcitabine

SYNONYM(S): gemcitabine hydrochloride, difluorodeoxycytidine, 2',2'-difluorodeoxycytidine, dFdC, LY 188011

COMMON TRADE NAME(S): GEMZAR®

CLASSIFICATION: antimetabolite

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Gemcitabine, a pyrimidine analog, is structurally similar to cytarabine, but has a wider spectrum of antitumour activity due to its different cellular pharmacology and mechanism of action.[1] Gemcitabine is metabolized intracellularly to two active metabolites, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). The cytotoxic effects of gemcitabine are exerted through incorporation of dFdCTP into DNA with the assistance of dFdCDP, resulting in inhibition of DNA synthesis and induction of apoptosis.[2,3] Gemcitabine is a radiation-sensitizing agent.[3] It is cell-cycle phase specific (S and G_1/S-phases).[3]

PHARMACOKINETICS:

Interpatient variability	3- to 4-fold interpatient and intrapatient variability[4]	
Oral absorption	no information found	
Distribution	widely distributed into tissues; also present in ascitic fluid.[5]	
	cross blood brain barrier?	no information found
	volume of distribution	IV infusion < 70 min: 50 L/m^2; IV infusion 70-285 min: 370 L/m^2
	plasma protein binding	< 10%[3]
Metabolism	Metabolized intracellularly by nucleoside kinases to active metabolites dFdCDP and dFdCTP; also metabolized intracellularly and extracellularly by cytidine deaminase to inactive metabolite difluorodeoxyuridine (dFdU).[3,4]	
	active metabolite(s)	dFdCDP, dFdCTP
	inactive metabolite(s)	dFdU
Excretion	mainly renal excretion	
	urine	92-98% over one week (89% as dFdU, < 10% as gemcitabine) after a single dose of 1000 mg/m^2 given over 30 minutes.[3]
	terminal half life	IV infusion <70 min: 0.7-1.6 h; IV infusion 70-285 min: 4.1-10.6 h
	clearance	IV infusion < 70 min: 41-92 L/h/m^2 (male) 31-69 L/h/m^2 (female)
Gender	decreased volume of distribution and clearance in women	
Elderly	decreased clearance and increased half-life with increasing age	

Adapted from reference[2] unless specified otherwise.

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USES:

Primary uses:
*Lung cancer, non-small cell
*Pancreatic cancer
Bladder cancer[10-12]

Other uses:
Breast cancer[6-8]
Cervical Cancer[9]
Head and neck cancer[13,14]
Lung cancer, small cell[15,16]
Lymphoma, cutaneous T-cell[17]
Lymphoma, Hodgkin's disease[18]
Mesothelioma[19]
Ovarian cancer[20]

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test but mutagenic in mammalian *in vitro* mutation test. Gemcitabine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[3]

Fertility: Decreased spermatogenesis and fertility in male mice.[3]

Pregnancy: FDA Pregnancy Category D.[3] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reaction (4%, severe 0.2%)[21]
blood/bone marrow febrile neutropenia	***anemia*** (68%, severe 8%)
	leukopenia (62%, severe 9%)
	neutropenia (63%, severe 25%); nadir 7-10 days, recovery within 7 days[22]
	thrombocytopenia (24%, severe 5%); nadir 7-10 days, recovery within 7 days[22]
cardiovascular (arrhythmia)	cardiac arrhythmia (2%, severe 0.2%)[21]
cardiovascular (general)	edema/peripheral edema (28%, severe 3%)[23]
coagulation	hemolytic uremic syndrome (0.3%); see paragraph following **Side Effects** table
constitutional symptoms	asthenia (42%, severe 2%)[21]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	fever (37%, severe <1%); see paragraph following **Side Effects** table
dermatology/skin	*extravasation hazard: irritant*[24-29]
	alopecia (14%)
	injection site reactions (4%)[30]; see paragraph following **Side Effects** table
	skin rash (25%, severe <1%); see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low moderate[31]
	constipation (8%, severe <1%)
	diarrhea (12%, severe <1%)
	nausea and vomiting (64%, severe 18%)
	stomatitis (8%, severe <1%)
hemorrhage	hematuria (31%, severe <1%)
hepatic	elevated alkaline phosphatase (55%, severe 9%); see paragraph following **Side Effects** table
	elevated AST (67%, severe 9%); see paragraph following **Side Effects** table
	elevated ALT (68%, severe 10%); see paragraph following **Side Effects** table
	elevated bilirubin (13%, severe 2%); see paragraph following **Side Effects** table
infection	infection (9%, severe 1%)
neurology	decreased level of consciousness (9%, severe <1%)
	peripheral neuropathy (3%)[32]
pain	pain (16%, severe 1%)
pulmonary	dyspnea (8%, severe 1%); see paragraph following **Side Effects** table
renal/genitourinary	elevated BUN (16%, severe 0%)
	elevated creatinine (7%, severe <1%)
	proteinuria (36%, severe <1%)
syndromes	flu-like symptoms (19%, severe 1%)[21]; see paragraph following **Side Effects** table
vascular	digital ischemia; see paragraph following **Side Effects** table
	peripheral vasculitis (<1%)[33,34]; see paragraph following **Side Effects** table

Adapted from reference[2] unless specified otherwise.

Dosing schedule and toxicity: Infusion time prolonged beyond 60 minutes has been shown to increase volume of distribution and has been associated with an increase in toxicity.[33] However, given in the context of a fixed dose rate (FDR) regimen, prolonged infusions have also been reported to produce a higher response rate than standard regimens in association with a higher intracellular accumulation of its active metabolite (dFdCTP).[35-38] Refer to protocol by which patient is being treated for direction regarding duration of infusion.

Hemolytic uremic syndrome has been infrequently reported[2] and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The syndrome can present either acutely with severe hemolysis, thrombocytopenia and rapidly progressive renal failure, or more insidiously with mild or no thrombocytopenia and slowly progressive renal failure. The etiology of hemolytic uremic syndrome is unknown.[39] The onset of the syndrome has been reported to occur during and shortly after gemcitabine therapy. If not treated promptly, the syndrome may result in irreversible renal failure requiring dialysis.[3] Therefore, patients with impaired renal function should be monitored closely while being treated with gemcitabine.[2,21]

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Elevated liver enzymes: Gemcitabine causes transient and reversible elevations of liver function enzymes in about two-thirds of patients. However, these increases are rarely of clinical significance and there is no evidence of increasing hepatic toxicity with either longer duration of gemcitabine treatment or cumulative dose.[2,21]

Fever/Flu-like symptoms: Fever of any severity was reported in 37% of patients. It is frequently associated with other flu-like symptoms such as headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia.[2] These symptoms are usually mild and transient, and rarely dose-limiting. The use of acetaminophen may provide symptomatic relief.[21]

Injection site reactions are reported in 4% of patients. Extravasation of gemcitabine does not cause tissue necrosis[30]. Anecdotally BC Cancer nurses have reported frequent injection site reactions to gemcitabine infusion. Although no further specific published reports have been identified, more recent practice guidelines have either reclassified gemcitabine as an irritant[25-28] or noted its ability to cause a chemical phlebitis.[29] Therefore, it has been proposed to reclassify gemcitabine as an irritant. See BC Cancer Policy Number III-20 Prevention and Management of Extravasation of Chemotherapy..

Severe pulmonary toxicity: Acute dyspnea may sometimes occur with gemcitabine therapy, but is usually self-limiting. However, severe pulmonary toxicities such as pulmonary edema, interstitial pneumonitis and adult respiratory distress syndrome have rarely been reported.[2] The symptoms are manifested as progressive dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on chest radiograph that are sometimes accompanied by fever and cough.[40-42] Pulmonary toxicities usually occur after several cycles of gemcitabine, but have also been seen as early as the first cycle. Risk factors for pulmonary toxicities include prior radiation to the mediastinum. Because of its structural similarities to cytarabine, gemcitabine is thought to cause lung injury by the same mechanism by inducing pulmonary capillary leakage.[40,41] Management of pulmonary toxicities consists of discontinuation of gemcitabine and early supportive care with bronchodilators, corticosteroids, diuretics, and/or oxygen.[2,40-42] Although pulmonary toxicities may be reversible with treatment, fatal recurrence of severe pulmonary symptoms was reported in one patient upon rechallenge with gemcitabine.[40]

***Skin rash*:** Typically mild to moderate in severity, with macular or finely granular maculopapular pruritic eruption on the trunk and extremities. It is not dose-limiting and usually responds to topical corticosteroids.[2,32] If needed, antihistamines such as diphenhydramine can be used.[32]

Vascular toxicity, including cases of thrombotic microangiopathy, veno-occlusive disease, and digital ischemic changes and necrosis, have been reported. The exact mechanism is unknown, although it is suggested to be more common and more severe after cumulative doses of 10,000 mg/m^2 or in the setting of combination therapy.[33,43-45]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
warfarin[46]	increased anticoagulant effect of warfarin	possibly decreased metabolism of warfarin and decreased hepatic synthesis of clotting factors	monitor INR carefully during and for 1-2 months after gemcitabine therapy; adjust warfarin dose as needed

SUPPLY AND STORAGE:

***Injection*:**
Accord Healthcare Inc. supplies gemcitabine hydrochloride as 1000 mg, and 2000 mg vials of sterile lyophilized powder. Store at room temperature.[47]

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Pfizer Canada /Hospira Healthcare Corporation supplies gemcitabine as 200 mg, 1000 mg, and 2000 mg vials of ready-to-use preservative-free aqueous solution in a concentration of 38 mg/mL. Refrigerate.[48]

Sandoz Canada Inc. supplies gemcitabine as 200 mg, 1000 mg, and 2000 mg vials of ready-to-use preservative-free aqueous solution in a concentration of 40 mg/mL. Refrigerate. [49]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: Solutions of reconstituted gemcitabine should not be refrigerated as crystallization may occur.[33]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	• ***over 30 min***[33]; can also be given over 60 min[6,10,12] • over greater than 60 minutes using a fixed dose rate (FDR) of ***10 mg/m²/min***[50,51]
Continuous infusion	investigational, has been used in clinical trials at lower dosages (100 mg/m²) over 24 h[52,53]
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical[54-57]	solutions are ***retained for 1-2 h*** after instillation

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or in patients with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle length:	
Intravenous:	2 weeks[6,58]:	2500 mg/m² (range 1250-2500 mg/m²) IV for one dose on day 1 (total dose per cycle 2500 mg/m² [range 1250-2500 mg/m²])

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	3 weeks[2,20]:	1250 mg/m^2 (range 800-1250 mg/m^2) IV for one dose on days 1 and 8 (total dose per cycle 2500 mg/m^2 [range 1600-2500 mg/m^2])
	4 weeks[2,32,59]:	***1000 mg/m^2*** (range 500-1250 mg/m^2) ***IV for one dose on days 1, 8 and 15*** (total dose per cycle 3000 mg/m^2 [range 1500-3750 mg/m^2])
	8 weeks[2,32]:	***1000 mg/m^2*** (range 500-1000 mg/m^2) ***IV for one dose on days 1, 8, 15, 22, 29, 36 and 42*** for the first cycle, then continue with the 4-week dose schedule (see above) (total dose per 8-week cycle 7000 mg/m^2 [range 3500-7000 mg/m^2])
	3 weeks[50,51]:	***900 mg/m^2*** (range 750-1200 mg/m^2) ***IV for one dose on days 1 and 8*** (total dose per cycle 1800 mg/m^2 [range 1500-2400 mg/m^2])
Intravesical:	***once*** to twice ***weekly***[54-57,60]:	induction: ***1000-2000 mg*** instilled ***intravesically once*** to twice ***weekly*** for 3 to 6 weeks (total dose per cycle 3000-24,000 mg)
	monthly[54-56,61]:	maintenance: ***1000-2000 mg*** instilled ***intravesically once monthly*** for up to 10 doses, starting 6 weeks after induction (total dose per cycle 10,000-20,000 mg)
Concurrent with radiation:	investigational, 100-400 mg/m^2 IV once daily every week[62,63]	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	No dosing recommendation available. However, caution should be used in patients with renal dysfunction.[64]	
Dosage in hepatic failure:	When used as a single agent in 4-week cycle treatment, no dose adjustment is required with elevated AST; may consider using a lower starting dose of 800 mg/m^2 with total bilirubin > 27 µmol/L.[64] Dosage adjustment for increased bilirubin does not appear to be necessary in regimens using fixed dose rate infusion of gemcitabine.[65]	
Dosage in dialysis:	no information found	
Children:	safety and effectiveness in children have not been established	

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REFERENCES:

1. Abratt RP, Bezwoda WR, Falkson G, et al. Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: a phase II study. JOCP 1994;12(8):1535-40.
2. Eli Lilly Canada Inc. Gemzar Product Monograph. Toronto, Ontario; 19 August 1999.
3. USP DI. Volume 1. Drug information for the health care professional. Update monographs. Gemcitabine. Micromedex, Inc., Available at: www.micromedex.com. Accessed 18 October 1999.
4. Storniolo AM, Allerheiligen SR, Pearce HL. Preclinical, pharmacologic, and phase I studies of gemcitabine. Sem Onc 1997;24(2 Suppl 7):S7-2-S7-7.
5. Delauter BJ, Ramanathan RK, Egorin MJ, et al. Pharmacokinetics of gemcitabine and 2 ',2 '-difluorodeoxyuridine in a patient with ascites. Pharmacother 2000;20(10):1204-1207.
6. Colomer R, Llombart A, Lluch A, et al. Paclitaxel/gemcitabine administered every two weeks in advanced breast cancer: preliminary results of a phase II trial. Sem Onc 2000;27(1 Suppl 2):20-4.
7. Carmichael J, Possinger K, Phillip P, et al. Advanced breast cancer: a phase II trial with gemcitabine. J Clin Oncol 1995;13(11):2731-2736.
8. Gennari A, Donati S, Danesi R, et al. The gemcitabine/epirubicin/paclitaxel combination in advanced breast cancer. Sem Onc 2000;27(1 Suppl 2):14-9.
9. González AD, López C, Mota A, et al. Neoadjuvant cisplatin/gemcitabine combination for locally advanced cervix carcinoma. Proceedings of the American Society of Clinical Oncology 2000;19:399a (abstract 1581).
10. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. JOCP 2000;18(17):3068-77.
11. Moore MJ, Winquist EW, Murray N, et al. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. JOCP 1999;17(9):2876-81.
12. Kaufman D, Raghavan D, Carducci M, et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. JOCP 2000;18(9):1921-7.
13. Fountzilas G, Athanassiades A, Kalogera-Fountzila A, et al. Paclitaxel in combination with carboplatin or gemcitabine for the treatment of advanced head and neck cancer. Sem Onc 1997;24(6 Suppl 19):S19-28-S19-32.
14. Khwaja R, Langer C, Padavic K, et al. Phase II evaluation of weekly cisplatin and gemcitabine in the treatment of incurable squamous cell carcinoma of the head and neck. Proceedings of the American Society of Clinical Oncology 2000;19:427a (abstract 1690).
15. De Marinis F, Cortesi E, Paoluzzi L, et al. Cisplatin, etoposide and gemcitabine in untreated patients with small cell lung cancer: preliminary results of a multi-institutional Phase II trial of GOL (Oncological Group of Lazio). Proceedings of the American Society of Clinical Oncology 2000;19:525a (abstract 2062).
16. Masters GA, Declerck L, Blanke CD, et al. Gemcitabine in refractory or relapsed small cell lung cancer - E1597: an ECOG Phase II trial. Proceedings of the American Society of Clinical Oncology 2000;19:527a (abstract 2070).
17. Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: Experience in 44 patients. JOCP 2000;18(13):2603-2606.
18. Santoro A, Bredenfeld H, Devizzi L, et al. Gemcitabine in the treatment of refractory Hodgkin's disease: Results of a multicenter phase II study. JOCP 2000;18(13):2615-2619.
19. Byrne MJ, Davidson JA, Musk AW, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: A phase II study. JOCP 1999;17(1):25-30.
20. Ozols RF. The role of gemcitabine in the treatment of ovarian cancer. Sem Onc 2000;27(1 Suppl 2):40-7.
21. Aapro MS, Martin C, Hatty S. Gemcitabine--a safety review. Anti-Cancer Drugs 1998;9(3):191-201.
22. Eli Lilly Canada. Gemcitabine data on file. Toronto, Ontario; 07 December, 2000.
23. Green MR. Gemcitabine safety overview. Sem Onc 1996;23(5 Suppl 10):32-5.
24. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 August 2014.
25. Oncology Nursing Society. Immediate complications of cytotoxic therapy. Chemotherapy and biotherapy guidelines. Pittsburgh, PA: Oncology Nursing Press, Inc; 2009.
26. Oncology Nursing Society. Infusion-related complications. Chemotherapy and biotherapy guidelines. Pittsburgh, PA: Oncology Nursing Press, Inc; 2014.
27. Payne AS, Savarese DMF. In: Basow DS, Drews RE, Ross ME, eds. Extravasation injury from chemotherapy and other non-neoplastic vesicants. Waltham, Massachusetts: UpToDate®; August 2014.
28. Lexicomp Online® Lexi-Drugs (database on the Internet). Management of drug extravasations. Lexi-Comp Inc., 25 July 2014. Available at: http://online.lexi.com. Accessed 3 September 2014.
29. Pérez Fidalgo JA, García Fabregat L, Cervantes A, et al. Management of chemotherapy extravasation: ESMO–EONS Clinical Practice Guidelines. Ann Oncol October 01, 2012;23(suppl 7):vii167-vii173.
30. Eli Lilly Canada. GEMZAR® product monograph. Toronto, Canada; 28 April 2014.
31. Anonymous. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1999;56(8):729-764.
32. Rothenberg ML, Moore MJ, Cripps MC, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol 1996;7(4):347-53.
33. Hospira Healthcare Corporation. Gemcitabine for injection, USP product monograph. Montreal, Quebec; 3 November 2008.

Developed: September 1994
Limited revision: 1 August 2021

34. Basow DS editor. Gemcitabine. UpToDate 18.2 ed. Waltham, Massachusetts: UpToDate®; 2010.
35. Veltkamp SA, Beijnen JH, Schellens JHM. Prolonged versus standard gemcitabine infusion: translation of molecular pharmacology to new treatment strategy. Oncologist March 1, 2008;13(3):261-276.
36. Pollera CF, Ceribelli A, Crecco M, et al. Prolonged infusion gemcitabine: a clinical phase I study at low- (300 mg/m2) and high-dose (875mg/m2) levels. Invest New Drugs 1997;15(2):115-121.
37. Kwan P, Mukhopadhyay P, Rastogi A, et al. A novel administration of gemcitabine (via constant dose rate) in combination with docetaxel in advanced non-small cell lung cancer. Proceedings of the American Society of Clinical Oncology 2000;19:507a (abstract 1985).
38. Dragovich T, Ramanathan RK, Remick S, et al. Phase II trial of a weekly 150-minute gemcitabine infusion in patients with biliary tree carcinomas. Proceedings of the American Society of Clinical Oncology 2000;19:296a (abstract 1159).
39. Gross M, Hiesse C, Kriaa F, et al. Severe hemolytic uremic syndrome in an advanced ovarian cancer patient treated with carboplatin and gemcitabine. Anti-Cancer Drugs 1999;10(6):533-6.
40. Pavlakis N, Bell DR, Millward MJ, et al. Fatal pulmonary toxicity resulting from treatment with gemcitabine. Cancer 1997;80(2):286-91.
41. Sauer-Heilborn A, Kath R, Schneider CP, et al. Severe non-haematological toxicity after treatment with gemcitabine. J Cancer Res Clin Oncol 1999;125(11):637-40.
42. Attar EC, Ervin T, Janicek M, et al. Side effects of chemotherapy. Case 3. Acute interstitial pneumonitis related to gemcitabine. JOCP 2000;18(3):697-8.
43. Dasanu CA. Gemcitabine: vascular toxicity and prothrombotic potential. Expert Opin Drug Saf 2008;7(6):703-716.
44. Holstein A, Batge R, Egberts E-. Gemcitabine induced digital ischaemia and necrosis. Eur J Cancer Care 2010;19:408-409.
45. Corella F, Dalmau J, Roe E, et al. Cutaneous vasculitis associated with gemcitabine therapy. Clin Exper Derm 2008;34:81-105.
46. Kinikar SA, Kolesar JM. Identification of a gemcitabine-warfarin interaction. Pharmacother 1999;19(11):1331-3.
47. Accord Healthcare Inc. Gemcitabine injection product monograph. Kirkland, Quebec; 24 March 2021.
48. Pfizer Canada Inc. Gemcitabine Injection (ready to use solution) product monograph. Kirkland, Quebec; 25 October 2018.
49. Sandoz Canada Inc. Gemcitabine hydrochloride solution for injection product monograph. Boucherville, Quebec; 14 August 2014.
50. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II Study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of Sarcoma Alliance for Research through Collaboration Study 002. J Clin Oncol July 1, 2007;25(19):2755-2763.
51. BC Cancer Agency Sarcoma Tumour Group. (SAAVGEMD) BCCA Protocol Summary for Second or Third Line Therapy for Soft Tissue Sarcomas using Gemcitabine and Docetaxel. Vancouver, British Columbia: BC Cancer Agency; 1 September 2010.
52. Eckel F, Lersch C, Assmann G, et al. Toxicity of a 24-hour infusion of gemcitabine in biliary tract and pancreatic cancer. Proceedings of the American Society of Clinical Oncology 2000;19:283a (abstract 1106).
53. Demir G, Buyukunal E, Ozguroglu M, et al. Weekly low dose continuous infusion of gemcitabine as a salvage therapy protocol in solid tumors. Proceedings of the American Society of Clinical Oncology 2000;19:665a (abstract 2623).
54. BC Cancer Genitourinary Tumour Group. (GUBGEM) BC Cancer Protocol Summary for Intravesical Therapy for Non-Muscle Invasive Bladder Cancer Using Gemcitabine. Vancouver, British Columbia: BC Cancer; 1 November 2019.
55. BC Cancer Genitourinary Tumour Group. (GUBGEMDOC) BC Cancer Protocol Summary for Intravesical Therapy for Non-Muscle Invasive Bladder Cancer Using Gemcitabine and Docetaxel. Vancouver, British Columbia: BC Cancer; 1 August 2021.
56. Skinner EC, Goldman B, Sakr WA, et al. SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical Bacillus Calmette-Guerin. J Urol 2013;190(4):1200-1204.
57. Steinberg RL, Thomas LJ, Brooks N, et al. Multi-institution evaluation of sequential intravesical gemcitabine and docetaxel as rescue therapy for non-muscle invasive bladder cancer. J Urol May 2020;203(5):902-909.
58. Sanchez-Rovira P, Jaen A, Gonzalez-Flores E, et al. Biweekly gemcitabine-adriamycin-paclitaxel combination in metastatic breast cancer patients: results from a phase II trial. Proceedings of the American Society of Clinical Oncology 2000;19:109a (abstract 423).
59. Burris HA,3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. JOCP 1997;15(6):2403-13.
60. Dalbagni G, Russo P, Bochner B, et al. Phase II trial of intravesical gemcitabine in Bacille Calmette-Guerin-refractory transitional cell carcinoma of the bladder. J Clin Oncol June 20, 2006;24(18):2729-2734.
61. Daniels MJ, Barry E, Milbar N, et al. An evaluation of monthly maintenance therapy among patients receiving intravesical combination gemcitabine/docetaxel for nonmuscle-invasive bladder cancer. Urol Oncol 2020;38(2):40.e17-40.e24.
62. Varveris C, Lyraraki E, Kachris S, et al. Phase I/II study of gemcitabine combined with cisplatin weekly and concurrent thoracic MV-radiotherapy for patients with stage IIIA/B non small cell lung cancer. Proceedings of the American Society of Clinical Oncology 2000;19:537a (abstract 2116).
63. Epelbaum R, Rosenblatt E, Nasrallah S, et al. A phase II study of gemcitabine combined with radiation therapy in patients with localized, unresectable pancreatic cancer. Proceedings of the American Society of Clinical Oncology 2000;19:265a (abstract 1029).
64. Venook AP, Egorin MJ, Rosner GL, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. JOCP 2000;18(14):2780-7.
65. Felici A, Di Segni S, Milella M, et al. Pharmacokinetics of gemcitabine at fixed-dose rate infusion in patients with normal and impaired hepatic function. Clin Pharmacokinet 2009;48(2):131-141.

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