DRUG NAME: Cisplatin

SYNONYM: CDDP,[1] cis-Diamminedichloroplatinum,[2] cis-dichlorodiammineplatinum(II),[3] cis-Patinum II,[2] DDP,[4]

COMMON TRADE NAME: PLATINOL®; PLATINOL-AQ®

CLASSIFICATION: Platinum compound[5]

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

MECHANISM OF ACTION:

Cisplatin is similar to the bifunctional alkylating agents. It covalently binds to DNA and disrupts DNA function.[6] After cisplatin enters the cells, the chloride ligands are replaced by water molecules.[7,8] This reaction results in the formation of positively charged platinum complexes that react with the nucleophilic sites on DNA.[2] These platinum complexes covalently bind to DNA bases using intra-strand and inter-strand cross-links creating cisplatin-DNA adducts thus preventing DNA, RNA and protein synthesis.[6] This action is cell cycle phase-nonspecific.[9] Cisplatin also has immunosuppressive, radiosensitizing, and antimicrobial properties.[2]

PHARMACOKINETICS:

Interpatient variability	systemic clearance resulting in variable blood platinum concentrations or AUCs[10]	
Oral Absorption	not absorbed[11]	
Distribution	rapidly diffuses into tissues[12]; highest concentrations found in the liver, prostate and kidney; rapidly distributed into pleural effusions and ascitic fluid	
	cross blood brain barrier?	not readily[9]
	volume of distribution[13]	ultrafilterable platinum*: 41 L/m²
	plasma protein binding	>90%[5,10,12]
Metabolism	undergoes non-enzymatic conversion to several inactive metabolites which are highly bound to plasma proteins[11]	
	active metabolite	yes
	inactive metabolite	yes[9]
Excretion	primarily in the urine[7]; urinary excretion of ultrafilterable platinum* was substantially greater after a 6-hour infusion than after a 15-minute injection[14]	
	urine	> 90%[7]; 25% excreted during the first 24 h[6]
	feces	insignificant
	terminal half life of ultrafilterable platinum*[7,10,15,16]	20-45 min
	terminal half life of total platinum*[7]	5 days or longer
	clearance	6.3 mL/min/kg
Gender	no clinically important differences found	
Elderly	no clinically important differences found	
Children	terminal half life of ultrafilterable platinum* < 1 h[11] terminal half life of total platinum* 24-72 h[11]	
Ethnicity	no clinically important differences found	

Adapted from standard reference[16] unless specified otherwise.

*Ultrafilterable platinum consists of non-protein-bound intact drug and metabolites, total platinum consists of all platinum species, both protein-bound or –unbound.[7] Note that it is the platinum that is usually measured.

USES:

Primary uses:
Adrenalcortical cancer
Anal cancer
* Bladder cancer
Brain cancer
Breast cancer
Cervical cancer
Esophageal cancer
Gallbladder cancer
Gastric cancer
Germ cell tumour
Gestational trophoblastic neoplasia
Head and neck cancer
Liver cancer
Lung cancer, non-small cell
Lung cancer, small cell
Lymphoma, Hodgkin's
Lymphoma, non-Hodgkin's
Mesothelioma
Neuroendocrine tumours
Nasopharyngeal cancer
Osteosarcoma
* Ovarian cancer
Salivary gland cancer
* Testicular cancer
Thymoma
Urothelial cancer

*Health Canada approved indication

Other uses:
Endometrial cancer[17]
Lymphoma, CNS[17]
Melanoma[17]
Multiple myeloma[17]
Pancreatic cancer[17]
Penile cancer[17]
Prostate cancer[17]

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to cisplatin[16] or other platinum-containing compounds.

Caution:
- Administer with caution to individuals with ***pre-existing renal impairment, myelosuppression*** or ***hearing impairment***.[13]
- ***Hydration*** is required to minimize nephrotoxicity.[13] The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose.[16] Hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis is used to effectively decrease cisplatin-induced nephrotoxicity.[7] Lower doses of cisplatin are given with less intensive hydration. For example, patients receiving doses of 35 mg/m^2 have been pre-treated with 500 mL NS over 1 hour, with no post-hydration. Patients receiving doses of 25 mg/m^2 have been pre-treated with vigorous oral hydration (e.g., 600-900 mL) the morning of treatment and 8 glasses (e.g., 2000 mL/day) daily for a few days following treatment. ***For a suggested hydration guideline, see the "Nephrotoxicity" paragraph following Side Effects table.***
- ***Inadvertent substitution*** of cisplatin for carboplatin can result in a potentially fatal overdosage.[2] Precautions should be taken to avoid overdosing such as writing the cisplatin dose as a daily dose, not as a total cisplatin dose used in one course of therapy. The manufacturer recommends that an alerting mechanism be instituted to verify any order for cisplatin >100 mg/m^2 per course every 3-4 weeks.

Carcinogenicity: found to have a carcinogenic effect in laboratory animals.[16]

Mutagenicity: shown to be a mild to moderate mutagen in the Ames test.[16]

Fertility: Cisplatin therapy is associated with at least temporary infertility in the majority of patients.[18] Among males receiving cisplatin for testicular cancer, almost all became azospermic within the first two cycles of therapy, but recovery of normal sperm morphology, motility, and sperm count occurred in 40% within 1.5-2 years.

Pregnancy: FDA Pregnancy Category D.[9] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., 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 as cisplatin is excreted in human milk.[9]

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.[19]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	hypersensitivity (rare); see paragraph following **Side Effects** table
auditory/hearing	***ototoxicity*** (31%); see paragraph following **Side Effects** table
	audiogram abnormalities (24%)
	tinnitus (9%)
	vestibular toxicity (rare)
blood/bone marrow/ febrile neutropenia	***myelosuppression*** (25-30%); WBC nadir 18-23 days (range 7.5-45), platelet nadir 18-23 days (range 7.5-45), recovery 39 days (range 13-62)
	anemia (25-30)%; see paragraph following **Side Effects** table
cardiovascular (arrhythmia)	arrhythmias[12]
	bradycardia (rare)
cardiovascular (general)	***vascular toxicities*** may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, or cerebral arteritis
constitutional symptoms	hiccoughs
dermatology/skin	*extravasation hazard*: irritant[20]
	alopecia (uncommon)
	rash (uncommon)
	local soft tissue toxicity (rare)
endocrine	glucose intolerance[12]
gastrointestinal	*emetogenic potential:* high[21]
	nausea and vomiting (> 90%); see paragraph following **Side Effects** table
	delayed nausea and vomiting; see paragraph following **Side Effects** table
	diarrhea

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	loss of taste
	pancreatitis[12]
	stomatitis[9]
hepatic	transient elevation of hepatic enzymes and bilirubin
metabolic/laboratory	elevated serum amylase
	electrolyte disturbances[2]; see paragraph following **Side Effects** table
	hyperuricemia
musculoskeletal	muscle cramps
neurology	autonomic neuropathy
	dorsal column myelopathy
	Lhermitte's sign
	neurotoxicity, usually peripheral neuropathies; see paragraph following **Side Effects** table
	seizures (rare)[6]
ocular/visual	visual impairment (rare)
	altered colour perception
	blurred vision
	cerebral blindness (infrequent)
	optic neuritis
	papilledema
renal/genitourinary	***nephrotoxicity*** (28-36%); see paragraph following **Side Effects** table
secondary malignancy	acute leukemia (rare)[9]
syndromes	inappropriate antidiuretic hormone syndrome
vascular	venous thromboembolic events[22-26]

Adapted from standard references[2,15,16] unless specified otherwise.

Anemia observed with cisplatin use may be caused by a decrease in erythropoietin or erythroid stem cells.[2] Cisplatin has been shown to sensitize red blood cells, sometimes resulting in a direct Coombs' positive hemolytic anemia.[16]

Electrolyte disturbances can be serious and mainly includes hypomagnesemia, hypocalcemia and hypokalemia. Hypophosphatemia and hyponatremia have occurred in some patients receiving cisplatin combination regimens.[2] These effects are due to renal tubular damage. Cisplatin greatly increases the urinary excretion of magnesium and calcium; increased excretion of potassium, zinc, copper and amino acids also occurs. Hypomagnesemia and or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany. Children may be at greater risk for developing hypomagnesemia.

Emetogenic effects are common with cisplatin therapy and may be serotonin-mediated.[10] **Acute** nausea and vomiting may occur within 1-6 (usually 2-3) hours after administration of cisplatin.[2] This early period is the most severe and usually lasts 8 hours, but can last up to 24 hours. Various levels of nausea, vomiting and anorexia may persist for up to 5-10 days. **Delayed** nausea and vomiting can occur 24 hours or longer following chemotherapy when complete emetic control had been attained on the day of cisplatin therapy. The incidence and severity of

cisplatin-induced nausea and vomiting appear to be increased in: females, the young, high doses, rapid infusion and combinations with other emetogenic drugs. Incidence and severity may be decreased in patients with a history of chronic alcohol use. **Acute** nausea and vomiting can be prevented by pre-treatment with a 5-HT_3 antagonist (e.g., granisetron, ondansetron) plus a corticosteroid; this can be continued for the first 24 hours following chemotherapy. **Delayed** nausea and vomiting should not routinely be treated with 5-HT_3 antagonists; although there is anecdotal evidence that some patients can benefit from 5-HT_3 antagonists[19], generally these agents are ineffective more than 24 hours after chemotherapy.[21] Corticosteroids are the cornerstone of the treatment for delayed nausea, although other combinations are widely used.[12] ***Refer to BC Cancer SCNAUSEA Protocol for details.***

Nephrotoxicity is a major concern when prescribing cisplatin. Renal dysfunction due to cisplatin may manifest as renal insufficiency, hypokalemia and hypomagnesemia. The risk for these adverse effects is related to the dose and interval of cisplatin and may be minimized by adequate hydration. Geriatric patients may also be at increased risk.

- The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose.[16] Others suggest hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis to effectively decrease cisplatin-induced nephrotoxicity.[7]

Refer to protocol by which patient is being treated. Numerous hydration regimens exist. Hydration regimens should take into account the following conditions for the patient ; adequate renal function, clinically euvolemic prior to administration of cisplatin, no contraindication to saline loading (e.g., uncompensated cardiac conditions, anasarca), and ability to comply with recommended oral hydration protocol, or expectation that volume status can be maintained (e.g., with fluids via enteral feeding tube or IV). Below is one suggested hydration regimen for adults.[27]

Cisplatin (mg/m^2)	*Hydration*	*Electrolyte Additives**	*Comments*
> 80	4000 mL* NS over 4 h	KCl 20 mEq $MgSO_4$ 1 g Mannitol 30 g	inpatient or medical daycare unit admission to monitor urine output
60-80	2000 mL* NS over 2 h	KCl 20 mEq $MgSO_4$ 1 g Mannitol 30 g	
40-60	1000 mL* NS over 1 h	KCl 10 mEq $MgSO_4$ 0.5 g	includes regimens with cisplatin administered over multiple days
<40	500 mL* NS over 30 min	none	includes regimens with cisplatin administered over multiple days

*Volume may include hydration associated with the administration of other drugs (e.g., other chemotherapy agents, supportive IV medications). The volumes and durations are minimum administration standards to accommodate the wide variation in clinical practice in delivery of cisplatin. They should be individualized based on the clinical situation, which may affect the hydration regimen and addition of electrolytes.

In children, for moderate to high-dose cisplatin give pre-hydration at 125mL/m^2/h for a minimum of 2 hours to increase urine output to >100 mL/m^2/h (> 3 mL/kg/h).[28] The hydration fluid most commonly used is D5NS + 20 mmol/L KCL.[29] In post-hydration, maintain urine output at 65-100 mL/m^2/h with oral/IV fluids.[28] Post-hydration is usually D5NS + 20 mmol/L KCL + 10 mmol/L MgS04 +/- mannitol.[29]

Nervous system effects are usually peripheral neuropathies and sensory in nature (e.g., parethesias of the upper and lower extremities).[2] They can also include motor difficulties (especially gait); reduced or absent deep-tendon reflexes and leg weakness may also occur. Peripheral neuropathy is cumulative and usually reversible, although recovery is often slow.[12] Geriatric patients may be at greater risk for these cisplatin-induced neuropathies. Muscle cramps have been reported, and usually occurred in patients with symptomatic peripheral neuropathy who received relatively high cumulative doses of cisplatin. Lhermitte's sign (a sensation during neck flexion resembling electric shock) often is present with cisplatin-induced neuropathy. The occurrence of Lhermitte's sign may coincide with the onset of peripheral neuropathies, and can last for 2-8 months. When signs of neuropathy occur, cisplatin should be discontinued.

Otic effects include tinnitus, with or without clinical hearing loss, and occasional deafness.[2] Ototoxicity is cumulative and irreversible and results from damage to the inner ear.[12] These effects may be more severe in children than in adults.[9] The manufacturer recommends that audiograms be performed prior to initiating therapy and prior to each

subsequent dose of drug.[16] Initially, there is loss of high frequency acuity (4000 to 8000 Hz). When acuity is affected in the range of speech, cisplatin should be discontinued under most circumstances and carboplatin substituted where appropriate. Ototoxicity appears to be dose related. Higher cumulative doses, higher individual doses and administration by IV bolus resulted in more severe ototoxicity,[30] corresponding with higher plasma levels of ultrafilterable platinum.[14] Ototoxicity may be enhanced in patients with prior or simultaneous cranial irradiation. Vestibular ototoxicity may increase with increasing cumulative dosage and may be more likely to occur in patients with pre-existing vestibular dysfunction.

Sensitivity reactions can include anaphylactoid reactions consisting of facial edema, flushing, wheezing or respiratory difficulties, tachycardia, and hypotension.[16] These reactions can occur within a few minutes after IV administration of cisplatin; diaphoresis, nasal stuffiness, rhinorrhea, conjunctivitis, generalized erythema, apprehension, and sensation of chest constriction may also occur. Cisplatin-induced anaphylactoid reactions usually have occurred after multiple cycles of cisplatin (e.g., at least 5 doses), but also can occur after the first dose.[2] There is a case report of a patient who experienced an anaphylaxis to cisplatin following nine previous uncomplicated cycles.[31] Some reactions may also be due to the mannitol that is given with cisplatin to prevent nephrotoxicity.[32] Occasionally, patients who experienced anaphylactoid reactions have been safely retreated with cisplatin following pre-treatment with corticosteroids and/or antihistamines; however, such prophylaxis is not uniformly effective in preventing recurrence.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
etoposide	synergistic antineoplastic activity against testicular, small cell lung and, non-small cell lung cancers	possible impaired elimination of etoposide in patients previously treated with cisplatin	some protocols are designed to take advantage of this effect; monitor toxicity closely
nephrotoxic drugs such as aminoglycoside antibiotics and amphotericin	increased risk of nephrotoxicity	cumulative nephrotoxoixity	use with extreme caution during or shortly after cisplatin
ototoxic drugs such as aminoglycoside antibiotics or loop diuretics (e.g., ethacrynic acid, furosemide)	increased risk of ototoxicity	cumulative ototoxicity	carefully monitor for signs of ototoxicity
phenytoin	decreased phenytoin serum levels	decreased absorption and/or increased metabolism of phenytoin	monitor serum levels of phenytoin
pyridoxine[33]	decrease in cisplatin activity	further investigation required	avoid concomitant use of pyridoxine with cisplatin
renally excreted drugs	increase the serum levels of renally excreted drugs	reduced renal function caused by cisplatin	monitor toxicity

Adapted from standard references[2] unless specified otherwise.

SUPPLY AND STORAGE:

Injection: Cisplatin is available as sterile, unpreserved; single-dose vials (10 mg/10 mL, 50 mg/50 mL and 100 mg/100 mL) at a concentration of 1 mg/mL.[16] Store at room temperature. Refrigeration or freezing will cause precipitation. Protect from light.

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:

- Do not use IV needles, syringes or sets that have aluminum components in the preparation or administration of cisplatin.[16] An interaction between aluminum and platinum will occur resulting in the formation of a black precipitate, accompanied with a loss of potency.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	not to be administered by the direct IV route
Intermittent infusion	over 15-30 minutes
Continuous infusion	over 6-24 hours (administration over 24 hours may decrease nausea, vomiting and nephrotoxicity)
Intraperitoneal	***hyperthermic intraperitoneal chemotherapy (HIPEC):*** pump solution into abdominal cavity and circulate as per protocol using hyperthermia pump; solutions and dwell time vary by protocol[34-38]
Intrapleural	has been used[5]
Intrathecal	no information found
Intra-arterial	has been used[15]
Intravesical	has been used[39]

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. Dosage may be reduced, delayed or discontinued in patients with bone marrow suppression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

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

Intravenous:

Cycle Length:	
1 week[40,41]:	***25-40 mg/m^2 IV on day 1*** (total dose per cycle 25-40 mg/m^2)
2 weeks[42]:	***30 mg/m^2 IV for one dose on days 1-3*** (total dose per cycle 90 mg/m^2)
3 weeks[43-48]:	***20-100 mg/m^2 IV on day 1*** (total dose per cycle 20-100 mg/m^2)

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

Cycle Length:

3 weeks[49]: ***60 mg/m^2 IV once daily for 2 consecutive days starting on day 1***
(total dose per cycle 120 mg/m^2)

3 weeks[50]: ***20 mg/m^2 IV for one dose on days 1 and 5***
(total dose per cycle 40 mg/m^2)

3 weeks[47]: ***30 mg/m^2 IV for one dose on days 1 and 8***
(total dose per cycle 60 mg/m^2)

3 weeks[51-56]: ***25 mg/m^2 IV for one dose on days 1-3***
(total dose per cycle 75 mg/m^2)

3 weeks[57-60]: ***20 mg/m^2 IV for one dose on days 1-5***
(total dose per cycle 100 mg/m^2)

4 weeks[61,62]: ***70-100 mg/m^2 IV on day 1***
(total dose per cycle 70-100 mg/m^2)

4 weeks[63,64]: ***25-30 mg/m^2 IV once daily for 3 consecutive days starting on day 1***
(total dose per cycle 75-90 mg/m^2)

6 weeks[65]: ***75 mg/m^2 IV for one dose on day 1***
(total dose per cycle 75 mg/m^2)

Concurrent radiation:

1 week[66]: ***40 mg/m^2 IV for one dose on day 1***
(total dose per cycle 40 mg/m^2)

2 weeks[60] ***100 mg/m^2 IV for one dose on day 1***
(total dose per cycle 100 mg/m^2)

3 weeks[67]: ***100 mg/m^2 IV for one dose on day 1***
(total dose per cycle 100 mg/m^2)

4 weeks[68]: ***25 mg/m^2 IV for 3 consecutive days starting on day 1***
(total dose per cycle 75 mg/m^2)

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: Suggested dose modifications:

Creatinine clearance (mL/min)	Dose
≥60	100%
45-59	75% cisplatin or go to carboplatin option (if available)

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

Cycle Length:

<45	hold cisplatin or delay with additional IV fluids or go to carboplatin option (if available)

Calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: no adjustment required

Dosage in dialysis: removable by dialysis, but only within 3 h of administration[9]

Children[2]***:***

Intravenous:

Cycle Length:

1 week: 30 mg/m^2 IV one dose on day 1

3 weeks: 90 mg/m^2 IV one dose on day 1

3-4 weeks: 60 mg/m^2 IV one dose on day 1 and day 2

REFERENCES:

1. Matsusaka S, Nagareda T, Yamasaki H. Does cisplatin (CDDP)function as a modulator of 5-fluorouracil (5-FU) antitumor action? A study based on a clinical trial. Cancer Chemotherapy Pharmacology 2005;55:387-392.
2. McEvoy GK, editor. AHFS 2004 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2004. p. 929-945.
3. Meyer KB, Madias NE. Cisplatin nephrotoxicity. Mineral & Electrolyte Metabolism. 1994;20(4):201-13.
4. Farris FF, Dedrick RL, King FG. Cisplatin pharmacokinetics: applications of a physiological model. Toxicology Letters 1988;43(1-3):117-37.
5. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. Fourth ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 256-259.
6. Chabner BA, Longo DL. Cancer chemotherapy and biotherapy. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 453-459.
7. Go R, Adjel A. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 1999;17(1):409-422.
8. Nieto Y. DNA-binding agents. Cancer Chemotherapy & Biological Response Modifiers 2003;Annual 21:Chapter 8.
9. Cisplatin. USP DI. Volume 1. Drug information for the health care professional. 20th ed. Englewood, Colorado: Micromedex, Inc.; 2002.
10. Murry DJ. Comparative clinical pharmacology of cisplatin and carboplatin. Pharmacotherapy 1997;17(5 Pt 2):140S-145S.
11. Crom WR, Glynn-Barnhart AM, Rodman JH, et al. Pharmacokinetics of Anticancer Drugs in Children. Clinical Pharmacokinetics 1987;12:179-182.
12. O'Dwyer P, Stevenson J, Johnson S. Clinical Pharmacokinetics and Administration of Established Platinum Drugs. Drugs 2000 2000;59 Suppl. 4:19-27.
13. Repchinsky C. Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2004. p. 431-432.
14. Belt RJ, Himmelstein KJ, Patton TF, et al. Pharmacokinetics of Non-Protein-Bound Platinum Species Following Adminisration of cis-Dichlorodiammineplatinum(II). Cancer Treatment Reports 1979;63(No. 9-10):1515-1521.
15. McEvoy GK, editor. AHFS 1989 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 1989. p. 929-945.
16. Mayne Pharma (Canada) Inc. Cisplatin product monograph. Montreal, Quebec; 2003.
17. Lexi-Drugs® (database on the Internet). Cisplatin. Lexi-Comp Inc., 16 March 2016. Available at: http://online.lexi.com. Accessed 31 March 2016.
18. Perry M, M.D. FACP. The Chemotherapy Source Book. Baltimore, Maryland: Williams & Wilkins; 1992. p. 405-409.
19. Christopher Lee MD. Personal Communication. Medical Oncologist, BC Cancer Agency, Fraser Valley Cancer Centre; 2005.

20. BC Cancer Agency Provincial Systemic Therapy Program. Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 February 2004.
21. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; May 1999.
22. Health Canada. Summary Safety Review - Cisplatin: Assessing the Potential Risk of Blood Clots in the Veins (venous thromboembolism). 12 February 2016. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/index-eng.php. Accessed 8 April 2016.
23. Health Canada. Health Product InfoWatch - Review Article: Cisplatin and venous thrombembolism. Health Canada Marketed Health Products Directorate, January 2015. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index-eng.php.
24. Hospira Healthcare Corporation. Cisplatin injection® product monograph. Saint-Laurent, Quebec; 23 July 2015.
25. Seng S, Liu Z, Chiu SK, et al. Risk of venous thromboembolism in patients with cancer treated with cisplatin: a systematic review and meta-analysis. J Clin Oncol 2012;30(35):4416-4426.
26. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 2011;29(25):3466-3473.
27. BC Cancer Agency Genitourinary Tumour Systemic Policy Group. Administration of cisplatin in the outpatient setting. BC Cancer Agency; 8 June 2000.
28. Ablin AR. Supportive Care of Children with Cancer. 2nd ed. Baltimore, Maryland: John Hopkins University Press; 1997.
29. Roberta Esau. Personal communication. Pharmacist, BC Children's Hospital; 10 May 2016.
30. Balis FM, Holcenberg JS, Bleyer WA. Clinical Pharmacokinetics of Commonly Used Anticancer Drugs. Clinical Pharmacokinetics 1983;8:202-232.
31. Basu R, Rajkumar A, Datta RN. Anaphylaxis to cisplatin following nine previous uncomplicated cycles. Int J Clin Oncol 2002;7:365-367.
32. Ackland SP, Hillcoat BL. Immediate hypersensitivity to mannitol: a potential cause of apparent hypersensitivity to cisplatin [letter]. Cancer Treatment Reports 1985;69(5):562-3.
33. Wiernik P, Yeap B, Vogl S, et al. Hexamethylmelamine and low or moderate dose cisplatin with or without pyridoxine for treatment of advanced ovarian carcinoma: a study of the Eastern Cooperative Oncology Group. Cancer Investigation 1992;10(1):1-9.
34. Yan TD, Deraco M, Baratti D, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: Multi-Institutional Experience. Journal of Clinical Oncology 2009;27(36):6237-6242.
35. Elias D, Gilly F, Boutitie F, et al. Peritoneal Colorectal Carcinomatosis Treated With Surgery and Perioperative Intraperitoneal Chemotherapy: Retrospective Analysis of 523 Patients From a Multicentric French Study. Journal of Clinical Oncology 2010;28(1):63-68.
36. HayesJordan A, Anderson PM. The diagnosis and management of desmoplastic small round cell tumor: a review. Curr.Opin.Oncol. 2011;23(4):385-389.
37. BC Cancer Agency Sarcoma Tumour Group. (SAHIPEC) BCCA Protocol Summary for Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Patients with Peritoneal Desmoplastic Small Round Cell Tumour (DSRCT) Using CISplatin. Vancouver, British Columbia: BC Cancer Agency; I January 2016.
38. BC Cancer Agency Gastrointestinal Tumour Group. (GIPMHIPEC) BCCA Protocol Summary for Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Patients with Peritoneal Mesothelioma Using DOXOrubicin, CISplatin, and PACLitaxel. Vancouver, British Columbia: BC Cancer Agency; I December 2015.
39. Dorr RT, Von-Hoff DD. Drug monographs. Cancer chemotherapy handbook. 2nd ed. Norwalk, Conneticut: Appleton and Lange; 1994. p. 286-293.
40. BC Cancer Agency Gastrointestinal Tumour Group. (GIFUC) BCCA Protocol summary for palliative chemotherapy for upper gastrointestinal tract cancer (gastric, esophageal, gall bladder carcinoma and cholangiocarcinoma) using infusional fluorouracil and cisplatin. Vancouver: BC Cancer Agency; 2001.
41. BC Cancer Agency Head and Neck Tumour Group. BCCA Protocol summary for recurrent and metastatic nasopharyngeal cancer using cisplatin and etoposide (HNDE). Vancouver: BC Cancer Agency; 2004.
42. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for treatment for high risk gestational trophoblastic cancer (GOTDHR). Vancouver: BC Cancer Agency; 2005.
43. BC Cancer Agency Genitourinary Tumour Group. BCCA Protocol summary for palliative therapy for urothelial carcinoma using cisplatin and gemcitabine (GUAVPG). Vancouver: BC Cancer Agency; 2002.
44. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for neo-adjuvant therapy for urothelial carcinoma using cisplatin and gemcitabine (UGUNAJPG). Vancouver: BC Cancer Agency; 2005.
45. BC Cancer Agency Genitourinary Tumour Group. (GUVIP2) BCCA Protocol Summary for Nonseminoma Consolidation/Salvage Protocol Using Etoposide, Cisplatin, Ifosfamide, Mesna. Vancouver, British Columbia: BC Cancer Agency; 1 February 2007.
46. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for adjuvant cisplatin and etoposide following resection of stage I, II and IIIA non-small cell lung cancer (LUAJEP). Vancouver: BC Cancer Agency; 2001.
47. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for treatment of advanced non-small cell lung cancer with platinum and gemcitabine (LUAVPG). Vancouver: BC Cancer Agency; 2005.
48. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for first-time treatment of advanced non-small cell lung cancer with cisplatin and docetaxel (LUCISDOC). Vancouver: BC Cancer Agency; 2005.
49. BC Cancer Agency Gynecology Tumour Group. BCCa protocol summary for treatment of small cell carcinoma of cervix using paclitaxel, cisplatin, etoposide and carboplatin with radiation (GOSMCC2). Vancouver: BC Cancer Agency; 2002.
50. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for consolidation/salvage treatment for germ cell carcinoma using vinblastine, cisplatin, ifosfamide and mesna (GUVEIP). Vancouver: BC Cancer Agency; 2003.

51. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for therapy of genitourinary small cell tumours with a platin and etoposide (GUSCPE). Vancouver: BC Cancer Agency; 2003.
52. BC Cancer Agency Head and Neck Tumour Group. BCCA Protocol summary for advanced head and neck cancer using cisplatin and fluorouracil (HNFUP). Vancouver: BC Cancer Agency; 2005.
53. BC Cancer Agency Head and Neck Tumour Group. Cisplatin and etoposide for recurrent and metastatic nasopharyngeal cancer. (HNDE). Vancouver: BC Cancer Agency; 1999.
54. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for treatment of limited stage small cell lung cancer alternating cyclophosphamide, doxorubicin and vincristine with etoposide and cisplatin plus early thoracic irradiation (LUALTL). Vancouver: BC Cancer Agency; 2002.
55. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for palliative therapy of selected solid tumours using cicplatin and etoposide (LUPE). Vancouver: BC Cancer Agency; 2004.
56. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for treatment of limited stage small-cell lung cancer with etoposide and cisplatin and early thoracic irradiation (LUPESL). Vancouver: BC Cancer Agency; 2004.
57. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for non-dysgerminomatous ovarian germ cell cancer using bleomycin, etoposide and cisplatin. Vancouver: BC Cancer Agency; 2001.
58. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for therapy of dysgerminomatous ovarian germ cell cancer using cisplatin and etoposide. Vancouver: BC Cancer Agency; 2001.
59. BC Cancer Agency Genitourinary Tumour Group. BCCA Protocol Summary for Bleomycin, Etoposide, Cisplatin for Nonseminoma Germ Cell Cancers (GUBEP). Vancouver: BC Cancer Agency; 2002.
60. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for therapy for etoposide - cisplatin protocol for germ cell cancers (GUBP). Vancouver: BC Cancer Agency; 2005.
61. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for therapy for transitional cell cancers of the urothelium using methotrexate, vinblastine, doxorubicin and cisplatin (GUMVAC). Vancouver: BC Cancer Agency; 2003.
62. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for combined chemotherapy and radiation treatment for stage 3 non-small cell lung cancer (LUCMT-1). Vancouver: BC Cancer Agency; 2005.
63. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol Summary for Treatment of Advanced/Recurrent Non-Small Cell Cancer of the Cervix with Cisplatin and Etoposide (GOCXADV). Vancouver: BC Cancer Agency; 2000.
64. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for combined modality therapy for sqamous cell cancer of the genitourinary system using fluorouracil and cisplatin (GUFUP). Vancouver: BC Cancer Agency; 2005.
65. BC Cancer Agency Neuro-Oncology Tumour group. BCCA Protocol Summary for adjuvant lomustine, cisplatin and vincristine in adult high-risk medulloblastoma or other primitive neuro-ectodermal tumour (PNET) - CNCCV. Vancouver: BC Cancer Agency; 2002.
66. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for treatment of high risk squamous cell carcinoma of cervix with concurrent cisplatin and radiation. (GOCXRADC). Vancouver: BC Cancer Agency; 2002.
67. BC Cancer Agency Head and Neck Tumour Group. BCCA Protocol summary for combined chemotherapy and radiation treatment for locally advanced squamous cell carcinoma of the head and neck (HNCMT2). Vancouver: BC Cancer Agency; 2004.
68. BC Cancer Agency Gastrointestinal Tumour Group. (GIEFUP) BCCA Protocol Summary for combined modality therapy for locally advanced esophageal cancer using cisplatin, infusional fluorouracil and radiation therapy. (GIEFUP). Vancouver: BC Cancer Agency; 2000.