DRUG NAME: VINCRISTINE

SYNONYM(S)[1,2]: LCR; Leurocristine; VCR

COMMON TRADE NAME(S)[1]: ONCOVIN®

CLASSIFICATION: Mitotic inhibitor, cytotoxic

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

MECHANISM OF ACTION:

Vincristine is a naturally occurring vinca alkaloid. Vinca alkaloids act as antimicrotubule agents that block mitosis by arresting cells in the metaphase.[3,4] These drugs act by preventing the polymerization of tubulin to form microtubules, as well as inducing depolymerization of formed tubules.[5] Vinca alkaloids are cell cycle phase-specific for M phase and S phase.

PHARMACOKINETICS:

Interpatient variability	large variation in terminal half-life and volume of distribution	
Oral Absorption	erratic	
Distribution	>90% distributed from blood into tissue within 15-30 min after injection	
	cross blood brain barrier?	no significant amount
	volume of distribution[6]	215 L/1.73 m^2
	plasma protein binding	75%
Metabolism[7]	hepatic cytochrome P-450 3A	
	active metabolite(s)	yes but not structurally identified
	inactive metabolite(s)	yes but not structurally identified
	urine	10-20% (12% within 72 h, 50% as metabolites)
	feces	about 80% (67% within 72 h, 40-50% as metabolites)
	terminal half life[8]	23-85 h
	clearance[6]	146 mL/min/1.73 m^2
Gender	no information found	
Elderly	no information found	
Children[9]	clearance more rapid than adults (terminal half life about 12–40 h)	
Ethnicity	no information found	

Adapted from reference 1, 3, 4, and 26 unless specified otherwise.

USES:

Primary uses:
Brain Tumours
*Breast cancer
*Cervical cancer
*Colorectal cancer
Ewing's sarcoma
Kaposi's sarcoma
*Leukemia, acute

Other uses:
Hepatoblastoma
Leukemia, chronic
Multiple myeloma
Mycosis fungoides
Retinoblastoma
Trophoblastic, gestational
Waldenstrom's macroglobulinemia

*Lung cancer, small cell
*Lymphoma, Hodgkin's disease
*Lymphoma, Non-Hodgkin's
*Melanoma
*Neuroblastoma
*Oteosarcoma
*Ovarian cancer
*Rhabdomyosarcoma
*Soft tissue sarcoma
*Wilm's tumour

*Health Canada approved indication

Adapted from reference 1, 3, 4, and 26 unless specified otherwise.

SPECIAL PRECAUTIONS:

Inadvertent administration of vincristine by the intrathecal (IT) route is nearly always **fatal** and is a medical emergency.[4,10,11] **All** vincristine doses dispensed should be labelled with an auxiliary label and a medication label, both stating **"WARNING: FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES"**.[10]

Contraindicated in: patients who have a history of hypersensitivity reaction to vincristine or vinca alkaloids,[12] patients with neurological disorders including hereditary motor and sensory neuropathy type 1, demyelinating Charcot-Marie-Tooth Syndrome and childhood poliomyelitis,[2] and patients receiving radiation to the liver. Vincristine has produced severe hepatic toxicity when given in conjunction with abdominal radiation therapy.[2,13]

Use with caution in: patients using other neurotoxic drugs[3] and patients using other ototoxic drugs including amino-glycosides, carboplatin, cisplatin and furosemide.[3]

Carcinogenicity: secondary malignancies have developed in patients receiving vincristine with other known carcinogenic drugs; but the contribution of vincristine is unknown.[3]

Mutagenicity: not mutagenic by *in vitro* and *in vivo* studies.[3]

Fertility: no information found.[4]

Pregnancy: FDA Pregnancy Category D.[14] 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 due to the potential secretion into breast milk.[14]

SIDE EFFECTS:

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in ***bold, italics*** I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
allergy/immunology[12]	anaphylaxis	I			
	edema	I			
auditory/hearing	dizziness		E	D	
	hearing impairment (temporary or permanent)		E	D	
	vertigo		E	D	
blood/bone marrow febrile neutropenia	anemia (rare)		E		
	leukopenia (rare)		E		
	thrombocytopenia (rare)		E		
cardiovascular (arrhythmia)	no information found				
cardiovascular (general)	coronary artery disease (rare)[15]			D	
	hypertension	I			
	hypotension	I			
coagulation	no information found				
constitutional symptoms	agitation	I			
	fever	I			
	sweating	I			
	weight loss			D	
dermatology/skin	*extravasation hazard*: vesicant	I			
	alopecia (20-70%)		E		
	rash (rare)	I			
endocrine	syndrome of inappropriate antidiuretic hormone (SIADH) (rare)		E		
gastrointestinal	*emetogenic potential:* non-emetogenic				
	abdominal cramps		E		
	constipation		E		
	diarrhea		E		
	oral ulceration		E		
	paralytic ileus		E		
	stomatitis		E		
metabolic/laboratory	hyperuricemia	I			
musculoskeletal	myoclonic jerks		E		
neurology	agitation	I			
	coma			D	

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in ***bold, italics*** I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
	depression		E		
	encephalopathy, progressive			D	
	hallucinations <5%[16]	I			
	insomnia	I			
	peripheral neuropathy		E		
	seizures	I			
ocular/visual	blurred		E		
	double vision		E		
	nystagmus		E	D	
	optic atrophy with blindness or transient cortical blindness			D	
	ptosis		E		
pain	finger pain			D	
	headache	I			
	jaw pain	I			
	joint pain	I			
	testicle pain			D	
	toe pain			D	
pulmonary	bronchospasm	I			
	hoarseness			D	
	shortness of breath, acute	I			
	vocal cord paralysis			D	
renal/genitourinary	dysuria		E		
	incontinence		E		
	nocturia		E		
	oliguria		E		
	polyuria		E		
	urinary retention		E		
sexual/reproductive function	amenorrhea			D	
	azoospermia			D	
	gonadal suppression			D	

Adapted from reference 1, 3, 4 and 26, unless specified otherwise.

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas), can be minimized with allopurinol and hydration. However, fluid restriction may be required for a patient showing signs of SIADH. If tumour lysis is reported in hospitalized patients the urine may be alkalinized by addition of sodium bicarbonate to the IV fluids.

Doses of uricosuric drugs, including probenecid and sulfinpyrazone may need to be increased while receiving vincristine therapy.[3]

Neurotoxicity involves peripheral, autonomic and central neuropathy. It is the primary and dose-limiting toxicity of vincristine. Most side effects are dose related and reversible, but neurotoxicity can persist for months after discontinuation of therapy in some patients, and in rare cases may be disabling.[17]

Infants are at a higher risk for experiencing vincristine-related neurotoxicity.[9]

Peripheral neuropathy is the most common type of neuropathy and develops in almost all patients.[3] Loss of deep tendon reflexes, peripheral paresthesias, pain and tingling can occur. If therapy is prolonged or high doses are administered, wrist and foot drop, ataxia, a slapping gait and difficulty in walking can occur. Cranial nerve toxicities may lead to vocal cord paresis or paralysis (hoarseness, weak voice), ocular motor nerve dysfunction (ptosis, strabismus), bilateral facial nerve palsies, or jaw pain. Severe jaw pain can occur within a few hours of the first dose of vincristine. The elderly are particularly prone.[2]
Autonomic neuropathy results in constipation (which can be severe), abdominal pain, urinary retention and paralytic ileus. Constipation may be associated with impaction of stool in the upper colon. This condition is responsive to high enemas and stimulant laxatives. Stool softeners and laxatives should be given prophylactically to prevent constipation.[3]
Central neuropathy includes headache, malaise, dizziness, seizures, mental depression, psychosis and SIADH.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
asparaginase	additive neurotoxicity	possible reduction in hepatic clearance of vincristine	give vincristine 12-24 hours before asparaginase
bleomycin	sequential administration of vincristine given before bleomycin can improve bleomycin efficacy	vincristine arrests cells in mitosis so that they are more susceptible to the actions of bleomycin	frequently used for therapeutic advantage
†carbamazepine[18]	possible decrease in vincristine plasma concentration	possible increase in metabolism (CYP3A4) of vincristine	observe clinical response when starting or stopping carbamazepine
ciprofloxacin[19]	possible decrease in antimicrobial effect of ciprofloxacin	possible decrease in oral absorption of ciprofloxacin	monitor for response to quinolone therapy

AGENT	EFFECT	MECHANISM	MANAGEMENT
*cyclosporin[20]	probable increase in vincristine toxicity	possible inhibition in metabolism (CYP3A4) of vincristine; possible decrease in clearance (blocking P-glycoprotein pump) of vincristine	if agents must be given concomitantly, monitor for vincristine toxicity
digoxin[18]	suspected decrease in digoxin plasma concentration	alteration in intestinal mucosa may decrease absorption of digoxin.	monitor for signs of reduction in digoxin pharmacologic effect
*erythromycin[20]	probable increase in vincristine toxicity	possible inhibition in metabolism (CYP3A4) of vincristine	if agents must be given concomitantly, monitor for vincristine toxicity; azithromycin may be substituted
*fluconazole[18]	probable increase in vincristine toxicity	possible inhibition in metabolism (CYP3A4) of vincristine	if agents must be given concomitantly, monitor for vincristine toxicity
*isoniazid[20]	possible increase in vincristine toxicity	possible inhibition in metabolism (CYP3A4) of vincristine	if agents must be given concomitantly, monitor for vincristine toxicity
*itraconazole[18,21-24]	probable increase in vincristine toxicity	possible inhibition in metabolism (CYP3A4) of vincristine	if agents must be given concomitantly, monitor for vincristine toxicity
*ketoconazole[18]	probable increase in vincristine toxicity	possible inhibition in metabolism (CYP3A4) of vincristine	if agents must be given concomitantly, monitor for vincristine toxicity
mitomycin	acute shortness of breath and severe bronchospasm has occurred following use of vincristine in patients who had received mitomycin simultaneously or within 2 weeks.	unknown	use with caution
nifedipine[18]	probable increase in vincristine toxicity	unknown	if agents must be given concomitantly, monitor for vincristine toxicity
phenytoin[2]	may reduce phenytoin concentrations resulting in seizures	unknown	monitor phenytoin serum levels
verapamil[20]	probable increase in vincristine toxicities	in vitro, vincristine and verapamil compete for plasma protein-binding sites	if agents must be given concomitantly, monitor for vincristine toxicity

Adapted from references 1, 3 unless specified otherwise

*Other drugs that inhibit the CYP3A4 enzyme system may result in an increase in vincristine levels.

†Other drugs that induce the CYP3A4 enzyme system may result in a decrease in vincristine levels.

SUPPLY AND STORAGE:

Supplied as a 1mg/mL solution. Available in 1, 2, and 5 mL vials. A formulation containing preservatives (methyparaben and propylparaben), and a preservative-free formulation are both available.

Vials should be stored in refrigerator and protected from light.

Unopened vials of the preservative-free formulation are stable for 5 days at room temperature and protected from light.[25]
Unopened vials of the preservative-free formulation that have been frozen for one month are stable.[25]

Opened vials of preservative-free formulation are stable for 8 hours.[4] Opened vials containing preservative are stable for 14 days if refrigerated and protected from light.[26]

SOLUTION PREPARATION AND COMPATIBILITY:

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

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous[11]	**NOT USED DUE TO THE RISK OF INADVERTENT INTRATHECAL ADMINISTRATION**
Intermittent infusion[11]	***50 mL NS or D5W over 5-15 min***
Continuous infusion[2,3]	has been given as continuous 4- or 5-day IV infusions for multiple myeloma
Intraperitoneal[2]	not used due to corrosive nature
Intrapleural	no information found
Intrathecal	**ABSOLUTELY CONTRAINDICATED; INTRATHECAL INJECTION CAN BE FATAL**
Intra-arterial[27-29]	has been used in head and neck tumours and in metastatic liver cancer
Intravesical	no information found

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 with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

Intravenous:

Cycle Length:

1-7 weeks	***0.8-1.4 mg/m^2 IV for one dose daily on day 1 (total dose per cycle 0.8-1.4 mg/m^2)***
2-4 weeks	***1-1.4 mg/m^2 IV for one dose daily on day 8 (total dose per cycle 2-2.8 mg/m^2)***
4 weeks:	***1.4 mg/m^2 IV for one dose on days 1 and 8 (total dose per cycle 2.8 mg/m^2)***
6 weeks:	***1.4 mg/m^2 IV for one dose on days 1 and 22 (total dose per cycle 2.8 mg/m^2)***
3 weeks:	***1.4 mg/m^2 IV for one dose daily on days 8 and 22 (total dose per cycle 2.8 mg/m^2)***
6 weeks:	***2 mg IV for one dose daily on days 1, 8 and 15 (total dose per cycle 6 mg/m^2)***

Some regimens may limit the total single dose of vincristine to 2 mg, especially on the weekly schedule.[9]

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[2] no modifications indicated

Dosage in hepatic failure[2]*:*

Bilirubin (micromol/L)	Vincristine dose
< 25	100%
26-50	50%
> 50	25%

Dosage in dialysis[4] small quantities of drug appear in dialysate

Dosage in neurotoxicity[30]

Neuropathy	Dose of vincristine
Areflexia	100%
Abnormal buttoning or writing	67%
Moderate motor neuropathy	50%
Severe motor neuropathy	Omit

Children:

Intravenous[9]:

Cycle Length:

1-3 weeks: 1-2 mg/m^2 for children older than one year[9]

1-3 weeks: 0.03-0.05 mg/kg for children up to one year old

Some regimens limit the total single dose of vincristine to 2 mg, especially on the weekly schedule.[9]

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