DRUG NAME: Daunorubicin

SYNONYM(S): daunomycin, DNR, rubidomycin

COMMON TRADE NAME(S): CERUBIDINE®

CLASSIFICATION: Anthracycline topoisomerase inhibitor

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

MECHANISM OF ACTION:

Daunorubicin is an anthracycline antibiotic which damages DNA by intercalating between base pairs resulting in uncoiling of the helix, ultimately inhibiting DNA synthesis and DNA-dependent RNA synthesis.[1] Daunorubicin may also act by inhibiting polymerase activity, affecting regulation of gene expression and generating free radicals. Cytotoxic activity is cell cycle phase non-specific, although it exerts maximal cytotoxic effects in the S-phase.

PHARMACOKINETICS:

Interpatient variability	no information found	
Distribution	highest levels in kidney, pancreas and liver; lowest levels in fat, crosses placenta.[2]	
	cross blood brain barrier?	no evidence that it crosses blood brain barrier
	volume of distribution[1,3]	1006-1725 L/m^2
	plasma protein binding	50-60%
Metabolism	extensively in liver and other tissues	
	active metabolite(s)	daunorubicinol (major metabolite – 60%)
	inactive metabolite(s)	yes
Excretion	urine	14-25%
	feces	hepatobiliary secretion in feces is predominant route of elimination (40%)
	terminal half life	18.5 h
	clearance	236-1117 mL/min/m^2
Gender	no information found	
Elderly	no information found	
Children	no information found	
Race	no information found	

Adapted from references[1,4] unless specified otherwise.

USES[1,4]:

Primary uses:
*Ewing's sarcoma
*Leukemia, acute lymphocytic
*Leukemia, acute myeloid
*Leukemia, chronic myelogenous
*Lymphoma, non-Hodgkin's

Other uses:
Kaposi's sarcoma
Lymphoma, Hodgkin's disease
*Lymphosacroma
Rhabdomyosarcoma
Wilm's tumour

*Health Canada Therapeutic Products Directorate approved indication

SPECIAL PRECAUTIONS:

Carcinogenicity: Potentially carcinogenic; mammary tumours and fibrosarcomas have been reported in rat and mice models.[1]

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* tests.[1] Daunorubicin is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: Gonadal suppression resulting in amenorrhea, zoospermia and testicular atrophy in male dogs.[5]

Pregnancy: FDA Pregnancy Category D.[5] 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.[5]

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	anaphylactoid-type I (rare)
	rash
blood/bone marrow febrile neutropenia	***myelosuppression;*** nadir 10-14 days, recovery 21-24 days
cardiovascular (arrhythmia)	arrhythmias due to acute cardiac toxicity – uncommon (ECG changes, AV block, bundle branch block)
	transient arrhythmias (6-30%)
	arrhythmias due to late onset cardiac toxicity
cardiovascular (general)	***congestive heart failure*** (rare, dose related)
	cardiomyopathy (rare, dose related)
	abnormal systolic function on echocardiogram (18-38%)[1]
dermatology/skin	*extravasation hazard*: vesicant
	alopecia (very common)
	facial flushing with rapid injection
	flare reaction (histamine release)
	hyperpigmentation
	nail changes
	pain on injection
	radiation recall reaction (rare)
gastrointestinal	*emetogenic potential*: moderate high
	diarrhea
	nausea and vomiting (85%)
	stomatitis[2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
metabolic/laboratory	hyperuricemia (during periods of active cell lysis)
neurology	neuropathy (13%)
renal/genitourinary	red colouration of urine

Adapted from references[1,5] unless specified otherwise.

Hyperuricemia may result from cell lysis by daunorubicin and may lead to electrolyte disturbances or acute renal failure.[6] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[7]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[8] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[9]

Tissue necrosis may be caused by extravasation of anthracyclines. These agents may bind to DNA and recycle locally to cause a progressive slough of tissue or ulceration over several weeks, requiring excision and skin grafting. For more details on the prevention and management of anthracycline extravasation, refer to BC Cancer Policy III-20 *Prevention and Management of Extravasation of Chemotherapy*.

Flare reaction is a painless local reaction along the vein or near the intact injection of anthracyclines. It is characterized by immediate red blotches, streaks and local wheals, probably due to histamine release.[10] Edema may sometimes occur.[10] Patients may or may not experience pruritus or irritation.[10] Symptoms usually subside with or without treatment 30 minutes after the infusion is stopped, although they may last for 1-2 hours and rarely more than 24 hours.[11] For more details on the prevention and management of anthracycline flare reaction, refer to BC Cancer Policy III-20 *Prevention and Management of Extravasation of Chemotherapy*.

Cardiotoxicity is thought to be due to free radical damage as myocardial tissue is susceptible to these highly reactive species.[12] Anthracycline cardiotoxicity may present with early or late effects.[13,14] The following information applies to all anthracyclines, anthracenediones and mitoxantrone.[12,14,15]

Early cardiotoxic effects are not dose-related and may present from mild ECG changes to life-threatening arrhythmias.[12,13,15] These events may occur during or immediately after a single dose of anthracycline treatment,[12,15] but do not predict subsequent development of delayed cardiotoxicity and are not considered indications for suspension of therapy.[12,13,15-18]

Late cardiotoxic effects, which are dose-related and clinically the most important type of cardiotoxic effect, present as reduced LVEF or symptomatic CHF, and typically occur weeks to years after completion of treatment.[12,14-17] Abnormalities in LVEF are associated with all the anthracyclines and their derivatives.[14] LVEF changes are related to the total cumulative dose, are irreversible and refractory to medical therapy. [12,19]

Prevention and treatment: Cardiac assessment should occur at baseline and throughout therapy. Monitor for symptomatic congestive heart failure (CHF) or reduced left ventricular ejection fraction (LVEF). Sensitive, non-invasive methods to measure LVEF include radionucleotide angiography (RNA), MUGA, or echocardiogram.[14] Late cardiotoxic effects may be prevented by stopping treatment with the associated anthracycline once patients have

reached the suggested maximum cumulative dose.[12,19] Management of anthracycline cardiotoxicity includes discontinuation of the drug and initiating standard treatment of CHF.[14]

Cardiotoxicity risk can be reduced but not eliminated with the use of alternative anthracyclines (i.e., epirubicin or liposomal doxorubicin) or by altering the frequency of administration (once a week vs. once every 3 weeks, or continuous infusion).[14] Cardioprotectant therapy with dexrazoxane may be considered for patients with cumulative doxorubicin-equivalent doses greater than 300 mg/m^2.[15,20,21]

Cumulative doses should be calculated using the following table, taking into account all previous anthracyclines or anthracenediones received during the patient's lifetime.

AGENT	SUGGESTED **CONVERSION FACTOR** TO **DOXORUBICIN DOSE**[22-24]*****	SUGGESTED **MONITORING THRESHOLD**[14,25-31]******
DAUNOrubicin	x 0.5-0.83	450 mg/m^2
DOXOrubicin	x 1	300 mg/m^2
epirubicin	x 0.5-0.67	600 mg/m^2
IDArubicin	x 2-5	150 mg/m^2
mitoXANTRONE	x 2.2-4	140 mg/m^2

* based on relative hematological toxicities[23]
** Treatment may continue beyond these doses in selected patients, if the clinician has considered the potential risks and benefits. The addition of dexrazoxane may be considered, and monitoring should be increased. Maximum tolerated doses are variable; some patients may tolerate doxorubicin equivalent doses exceeding 1000 mg/m^2 while other patients exhibit symptomatic CHF at doxorubicin equivalent doses less than 300 mg/m^2.

INTERACTIONS:

AGENT	**EFFECT**	**MECHANISM**	**MANAGEMENT**
ciprofloxacin[32]	may decrease the effect of ciprofloxacin	may decrease ciprofloxacin absorption by altering the intestinal mucosa	monitor patient, increase ciprofloxacin dose if necessary

SUPPLY AND STORAGE:

Injection[1,4]: 20 mg vial. Store at room temperature.

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:
- Clear, red solution[1]. Colour change from red to blue-purple indicates decomposition; discard affected solution.[33]
- Contact between daunorubicin and aluminium may result in darkening of the solution and formation of black patches on the aluminium surface after 12-24 hours.[33] Daunorubicin should not be stored in contact with aluminium but it may be injected safely through an aluminium-hubbed needle.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	not used due to corrosive nature[1]
Intramuscular	not used due to corrosive nature[1]
Direct intravenous	preferred method due to need for frequent monitoring for signs of extravasation.[1] May be diluted with 10 to 15 mL of NS and injected over 2-3 min using a small (21 or 23) gauge needle into tubing of running IV. ***Give via syringe using side arm method; dilute in 5-15 mL NS and infuse into tubing of a free flowing IC at a rate of 20 mg every 1-3 min.*** Push slowly so that drip of IV solution does not stop or reverse. Check for blood return before administration and after every 2-3 mL of drug. If no blood return, stop the injection and assess the IV site. Flush with a 20 mL solution after administration to clear any remaining drug from tubing.
Intermittent infusion	***over 30***-45 ***min***[34-36]
Continuous infusion	dilute in a convenient volume of NS or D5W and infuse through a central venous catheter
Intraperitoneal	not used due to corrosive nature[1]
Intrapleural	not used due to corrosive nature[1]
Intrathecal	not used due to corrosive nature[1]
Intra-arterial	no information available on this route
Intravesical	no information available on this route

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:	3-4 weeks:	*initial therapy*: *monotherapy* 30-60mg/m^2 IV once daily for 3-6 consecutive days staring on day 1 (total dose per cycle 90-360 mg/m^2) maximum dose during initial treatment[4]: 45-600mg/m^2 *combination therapy*[1] 45 mg/m^2 (30 mg/m^2 if > 60 y old) IV once daily for 2-3 consecutive days starting on day 1 (total dose per cycle 90-135 mg/m^2 [60-90 mg/m^2 if > 60 y old]) maximum dose[4]: 12-20mg/kg per treatment period
	1 week:	*maintenance*[4]: 1mg/kg IV for one dose on day 1

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

Cycle Length:

Suggested maximum lifetime dose[25]: 900 mg/m^2 in adults with normal cardiac function, lower doses are recommended if in combination with thoracic radiation or prior anthracycline therapy**.** Careful cardiac monitoring is important, as cardiotoxicity may occasionally occur at lower cumulative doses. If tumour is responding when lifetime dose is reached, a cardiac consultation should be obtained before continuing treatment.

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: reduce dose by 50% if creatinine greater than 265 micromol/L

Dosage in hepatic failure:

Bilirubin (micromol/L)	% usual dose
26-51	75%
52-85	50%
> 85	not recommended

Dosage in dialysis: no information found

Children:

Cycle Length:

Intravenous:

3-4 weeks[5]: > *2 y old* 25-45mg/m^2 IV, frequency of administration dependent on specific regimen employed

< *2 y old* or BSA < 0.5 m^2 calculate dose based on BW rather than BSA (mg/kg dose can be approximated by dividing the mg/m^2 dose by 30)

Maximum dose[5]:
BW 20 kg: 600 mg/m^2
BW 30 kg: 750 mg/m^2
BW 10 kg: 500 mg/m^2

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