Drug Monograph

A - Drug Name

DOXOrubicin

COMMON TRADE NAME(S): Adriamycin®

back to top

B - Mechanism of Action and Pharmacokinetics

Doxorubicin, an anthracycline antibiotic, damages DNA by intercalation into DNA, metal ion chelation, or by generation of free radicals. Doxorubicin has also been shown to inhibit DNA topoisomerase II which is critical to DNA function. Cytotoxic activity is cell cycle phase non-specific.

Distribution	Extensively distributed into tissues.	
	Cross blood brain barrier?	no
	PPB	50 - 85 %
Metabolism	Liver (major site) and other tissues. Clearance is reduced, with elevated levels of doxorubicin and its metabolites, in patients with hepatic dysfunction especially if bilirubin elevated.	
	Active metabolites	Doxorubicinol (major metabolite)
	Inactive metabolites	yes
Elimination	Elimination primarily via liver and biliary system. Predominantly in bile, 40-50% in feces within 7 days (50% unchanged).	
	Clearance is reduced in obese patients (e.g. >130% of ideal body weight).	

Urine	4-5% over 5 days.
Half-life	(terminal) 20-48 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Acute lymphocytic leukemia
- Acute myeloblastic leukemia
- Bladder cancer (intravenous and intravesical)
- Breast cancer
- Gastric cancer
- Head and neck cancer, squamous cell
- Hodgkin lymphoma
- Lung cancer (small cell and non-small cell)
- Neuroblastoma
- Non-Hodgkin lymphoma
- Osteogenic sarcoma
- Gynecologic cancer/sarcoma
- Sarcoma, soft tissue
- Testicular cancer
- Thyroid cancer
- Wilms' tumour

Other Uses:

- Adrenocortical cancer
- Neuroendocrine tumour
- Hepatocellular cancer
- Renal cell cancer
- Multiple myeloma
- Thymoma
- Unknown primary tumour
- Small cell carcinomas
- Ewing sarcoma

back to top

D - Adverse Effects

Emetogenic Potential: Moderate (< 60 mg/m2)
High (≥ 60 mg/m2)

Extravasation Potential: Vesicant

Incidences below are based on various sources. Incidences reported from the doxorubicin treatment arm (70 mg/m^2) in a phase III metastatic breast cancer study with anthracycline-naïve and mitoxantrone-naïve patients are marked with an asterisk (*).

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<3%) (acute)	I E
	Cardiotoxicity (<10%) * (symptomatic)	E D L
	ECG changes (20-30%)	I E
	Myocarditis (also pericarditis; rare)	E D
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (97%) * (complete in most patients)	E
	Hand-foot syndrome	E
	Photosensitivity	I E
	Radiation recall reaction (rare)	I E
	Rash (<10%) (may be severe)	E
	Skin hyperpigmentation (also mucosa, nails; rare)	D
Gastrointestinal	Anorexia (30%) *	I E
	Diarrhea (21%) * (may be severe with cytarabine)	I E
	Mucositis (62%) * (10% severe)	E
	Nausea, vomiting (75%) * (26% severe)	I E
Hematological	Myelosuppression ± infection, bleeding (86%) * (severe)	E
Hepatobiliary	↑ LFTs (rare; may be severe)	E
Hypersensitivity	Hypersensitivity (rare)	I
	Infusion related reaction (doxorubicin flare - histamine release; skin rash, fever, chills)	I E
Injection site	Phlebitis (15%) * (chemical)	I
Metabolic / Endocrine	Hyperuricemia (during periods of active cell lysis)	I
Neoplastic	Leukemia (secondary) (3%)	L
Ophthalmic	Conjunctivitis (rare)	E

	Watering eyes (rare)	E
Urinary	Cystitis (chemical, with bladder instillation)	I E
	Urine discoloration (red, for 1-2 days)	I

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for DOXOrubicin include alopecia, myelosuppression ± infection, bleeding, nausea/vomiting, mucositis, anorexia, diarrhea, phlebitis, and ECG changes.

Myelosuppression is the most common dose-limiting toxicity; severe and fatal infections may occur.

Anthracycline-induced **cardiotoxicity** may manifest either as an initial acute effect with transient sinus tachycardia and/or ECG abnormalities, or a later cumulative, dose-dependent cardiomyopathy. The acute electrocardiographic changes are usually reversible, unrelated to total dose and do not predict subsequent development of delayed cardiotoxicity.

The more serious cardiotoxicity is a **dose-dependent cardiomyopathy**. The onset of cardiomyopathy may be delayed, occurring 2-3 months or up to years after therapy. The incidence of drug-induced congestive heart failure at cumulative doses of 300 mg/m^2 is 1-2% in contrast to 20% incidence with cumulative dose >550 mg/m^2. The usual maximum cumulative dose of doxorubicin is 550 mg/m^2 (q21d cycles); however, certain patients (prior mediastinal radiation, prior anthracyclines or trastuzumab, older age, active or dormant cardiovascular disease, including hypertension) are at higher risk and may develop cardiotoxicity at lower cumulative doses of doxorubicin. These patients should receive cumulative doses of doxorubicin <400mg/m^2. In adults with risk factors, cardiac function monitoring (echocardiogram or MUGA scan) should be performed before treatment and periodically throughout treatment. All patients who have received total cumulative doses of 450 mg/m^2 and in whom further therapy with doxorubicin is indicated should undergo cardiac assessment before continuing treatment. The risk of cardiotoxicity may be lower with weekly regimens; total cumulative doses should not exceed 700mg/m^2 even with weekly regimens. Dexrazoxane may be used as a cardioprotectant in patients with advanced or metastatic cancer who are at risk of developing cardiotoxicity when receiving chemotherapy containing doxorubicin.

Children less than 15 years of age are more likely to develop CHF from cumulative doses greater than 550 mg/m^2 than those patients aged 15 to 40 years.

Patients at risk of **tumour lysis syndrome** should have adequate prophylaxis and be monitored closely.

Erythematous streaking (a histamine release phenomena) along the vein proximal to the site of injection has been reported and usually subsides within 30 minutes. The injection may be continued,

more slowly in the same site or may be changed to another site. Diphenhydramine 25 mg or hydrocortisone 100 mg, by slow IV push over 5 minutes into the IV line may hasten clearing of the reaction.

The tissue necrosis that occurs with **extravasation** may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected. Local protocols should be followed regarding management; dexrazoxane has been studied in the treatment of anthracycline extravasation (Mouridsen et al).

Doxorubicin has the potential to enhance **radiation injury** to tissues. The skin is the site most commonly affected, resulting in erythema followed by dry desquamation. Skin reactions generally occur only if the drug is given within 7 days of the radiation. Rarely, reactions after 30 days have been noted. Skin involvement, while unpleasant, is not as debilitating as in the case for internal organs. Enhancement of radiation injury to the esophagus and gastrointestinal tract is the most severe when the drug and the radiation are given concomitantly. Recurrent injury to a previously irradiated site may occur weeks to months following radiation.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

May need to consider lower starting doses or longer intervals between cycles for heavily pretreated patients, children, elderly, obese patients (e.g. > 130% of ideal body weight), or patients with bone marrow depression due to cytotoxic/radiation therapy, or tumour infiltration.

Patients should recover from toxicity before retreatment (i.e. stomatitis, neutropenia, thrombocytopenia, etc.).

Adults:

Intravenous:

- q1w: 10-20 mg/m^2 bolus
- q3w: 60-75 mg/m^2 bolus (40-60mg/m^2 when used in combination)\
- q4w: 20-30 mg/m^2/day bolus for 3 consecutive days

Intravesical:

q1w: 50-80 mg via bladder instillation (in 50-100mL), retained 1-2 hours, weekly x 4 then monthly. Voided urine should be inactivated with hypochlorite solution.

Maximum lifetime dose:*

	3-weekly regimen	Weekly regimen
Cardiac risk factors	400 mg/m^2	550 mg/m^2
No cardiac risk factor	550 mg/m^2	700 mg/m^2

*includes all anthracyclines and anthracenediones

Dosage with Toxicity:

Modify according to protocol by which patient is being treated.

Suggested dose levels: 75, 60, 50, 40 mg/m^2.

Worst Toxicity / Counts in Prior Cycle	Doxorubicin Dose for Next Cycle
Febrile Neutropenia / Thrombocytopenic bleeding / ANC grade 4 ≥ 7 days	↓ 1 dose level*
Cardiotoxicity**	Discontinue
Grade 3 related organ	↓ 1 dose level*
Grade 4 related organ	Discontinue

*Do not start new cycle until organ toxicity ≤ grade 2, platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x 10^9/L

**including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, a greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.

Management of Infusion-related reactions with Anthracyclines:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms.	• Consider pre-medications and administering at a slower infusion rate.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital symptoms have been affected. • Consider desensitization if therapy is necessary.

Dosage with Hepatic Impairment:

Doxorubicin is contraindicated in patients with severe hepatic impairment, and doses should be modified for mild-moderate impairment.

Bilirubin (µmol/L)		AST/ALT	% Usual Dose
1-2x ULN			50%
2-4x ULN	and/or	5-10 x ULN	25%
>4xULN	and/or	> 10 x ULN	OMIT

Dosage with Renal Impairment:

No adjustment required

Dosage in the elderly:

Use with caution.

Children:

At higher risk of secondary leukemia. Children and adolescents are at an increased risk of developing delayed cardiotoxicity (up to 15 years after treatment). Females may have a higher risk than males. Increased monitoring is required.

back to top

F - Administration Guidelines

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline). Depending on the dose volume and vein condition, administer the dose between 3 to 10 minutes to minimize thrombosis risk or extravasation.
- Do not admix with other drugs unless data are available; precipitates with fluorouracil and heparin.
- Avoid contact with alkaline solutions as this can lead to hydrolysis of doxorubicin.
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly as per local guidelines and should include application of ice to the affected area.
- Store vials under refrigeration (2 to 8ºC) and protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components, other anthracyclines or anthracenediones (i.e. epirubicin, daunorubicin, mitoxantrone or mitomycin C)
- Persistent myelosuppression induced by chemotherapy or radiation
- Severe hepatic impairment
- Severe myocardial insufficiency, arrhythmias or history of cardiac disease or recent myocardial infarction
- Previous treatment with maximum cumulative doses of doxorubicin, other anthracyclines or anthracenediones
- Avoid intravesicular use in patients with hematuria, urinary tract infections or bladder inflammation

Other Warnings/Precautions:

- Avoid the use of live vaccines; use may result in serious infections in immunocompromised patients.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Embryotoxicity: Yes
  Doxorubicin is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **6.5 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **3.5 months** after the last dose.
- Excretion into breast milk: Yes
  Breastfeeding is not recommended during treatment and for at least **10 days** after the last dose.
- Fertility effects: Yes
  May be partially reversible.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
barbiturates	↓ therapeutic effects of doxorubicin	↑ clearance of doxorubicin	monitor if barbiturates initiated or discontinued
cyclophosphamide	exacerbation of cyclophosphamide-induced hemorrhagic cystitis	unknown	Caution
cyclophosphamide	cardiotoxicity	Additive	Caution; refer to regimen by which patient is treated
digoxin	↓ digoxin levels; interaction may occur several days after treatment	decreased digoxin absorption	monitor digoxin levels and patient
mercaptopurine	↑ hepatotoxicity	Uncertain	monitor
quinolones	↓ antimicrobial effects of quinolones	↓ Quinolones absorption	monitor, may need to modify dose of quinolones
cytarabine	typhlitis	Uncertain	Treat appropriately
streptozocin	↑ toxicity of doxorubicin	liver damage by streptozocin decreases metabolism of doxorubicin	Caution
zidovudine	↓ effect of zidovudine	doxorubicin decreases intracellular activation	Avoid
stavudine	↓ effect of stavudine	Inhibits stavudine phosphorylation/metabolism	Avoid
trastuzumab	↑ cardiotoxicity	Additive	Avoid anthracycline-based therapy for up to 28 weeks after stopping trastuzumab
bevacizumab	↑ cardiotoxicity effect of anthracyclines	Unknown	Avoid
paclitaxel followed by doxorubicin	↑ neutropenia and stomatitis	↓ doxorubicin clearance	use paclitaxel after doxorubicin
dactinomycin	↑ radiation recall pneumonitis	Additive effects	Caution

phenytoin	↓ phenytoin levels	Unknown	Caution, check levels
cyclosporine	↑ doxorubicin plasma level up to 55%, hematologic and neuro toxicity reported	↓ doxorubicin clearance/ metabolism	Caution; avoid if possible
calcium channel blockers (e.g. verapamil)	↑ cardiotoxicity	Additive	Avoid
high dose progesterone (e.g. up to 10 g over 24 h)	↑ hematologic toxicity	Unknown	Caution
sorafenib	↑ doxorubicin toxicity	↑ doxorubicin exposure (up to 47%)	Caution; combination not indicated
p-glycoprotein inhibitors (i.e. quinidine, verapamil, cyclosporine)	↑ doxorubicin toxicity	↑ doxorubicin exposure (up to 2x)	Caution; monitor

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose
Liver function tests	Baseline and before each cycle
Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors (including prior trastuzumab or patients at or above threshold dose levels)	Baseline and as clinically indicated
Clinical toxicity assessment for infection, bleeding, stomatitis, nausea, vomiting, injection site reactions, cardiac effects, dermatologic effects, hyperuricemia	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

K - References

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October 2023 Updated Pregnancy/breastfeeding section

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top