DRUG NAME: Mitoxantrone

SYNONYM(S): Dihydroxyanthracenedione,[1] DHAD[1,2]

COMMON TRADE NAME(S): Mitoxantrone injection, NOVANTRONE® (USA)

CLASSIFICATION: intercalating agent-antitumour antibiotic

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

MECHANISM OF ACTION:

Mitoxantrone is a synthetic anthracenedione that is structurally similar to doxorubicin and daunorubicin.[2,3] It was synthesized with the goal to reduce anthracycline side effects, particularly cardiotoxicity.[4] Mitoxantrone inhibits DNA repair by inhibiting topoisomerase II[3,5] which results in fragmentation of DNA.[6] Mitoxantrone is an immunosuppressive agent[3,5] that may also generate free radicals, inhibit protein kinase C, cause electrostatic DNA cross-links, and induce apoptosis.[2] Although maximally cytotoxic in the S-phase, mitoxantrone is not cell cycle phase-specific.[2,7] Cross-resistance with anthracyclines has been demonstrated.[2]

PHARMACOKINETICS:

Oral Absorption	poor[5]	
Distribution	extensive tissue distribution; 3X greater AUC in patients with severe hepatic dysfunction	
	cross blood brain barrier?	not to an appreciable extent
	volume of distribution[5]	14 L/kg; distributes into pleural fluid, kidney, thyroid, liver, heart, and red blood cells
	plasma protein binding[5]	>95%; 76% to albumin
Metabolism	hepatic, pathways undetermined	
	active metabolite(s)	no information found
	inactive metabolite(s)[8]	yes
Excretion	urine[2,5]	6-11%; 65% unchanged
	feces[5]	25%; 65% unchanged
	terminal half life	23-215 h; prolonged by hepatic impairment
	clearance[9]	10.9-37.4 L/hr/m^2
Elderly	decreased clearance	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

*Leukemia, including acute non-lymphocytic
Prostate cancer[10]

Other uses:

*Breast cancer
*Hepatoma
*Lymphoma
Pediatric sarcoma[5]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to anthracyclines or mitoxantrone[3]
- severe hepatic impairment[3]*;* safety in patients with hepatic impairment has not been established[3]; reduced dosage has been used[3]

Caution: when used in combination regimens, the initial dose should be reduced by 2-4 mg/m^2 below the recommended dose for single-agent usage[3]

Cardiac toxicity is a risk of mitoxantrone therapy that may be manifested by acute or delayed events. Risk factors for developing mitoxantrone-induced cardiotoxicity include[3]:
- high cumulative dose
- previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease [left ventricular ejection fraction (LVEF) <50% or a clinically-significant reduction in LVEF]
- concomitant use of other cardiotoxic drugs.

Carcinogenicity: Studies not preformed to date.[3] Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) have been reported when used alone but more so when used with other antineoplastic agents and/or radiation.[3]

Mutagenicity: Mutagenic in microbial mutagenicity tests.[3] Mitoxantrone is clastogenic in mammalian *in vivo* chromosome tests; at doses approximating clinical use levels, the clastogenic effect is reversible.[3]

Fertility: Amenorrhea and a typically reversible reduction in spermatogenesis have been reported.[3,8,11] At the highest tolerated doses allowing evaluation of reproduction in rats, mitoxantrone had no effect on fertility.[3]

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 (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 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.[12]

ORGAN SITE	**SIDE EFFECT** Mitoxantrone is typically well tolerated at standard doses.[3]
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reactions; including anaphylaxis (<1%)
blood/bone marrow/ febrile neutropenia	***anemia*** (5-75%)
	leukopenia (9-100%); nadir typically occurs on day 10 with recovery by day 21
	myelosuppression; dose-limiting; severe myelosuppression is rare
	thrombocytopenia (33-39%)
cardiovascular	arrhythmia (3-18%); including sinus bradycardia

ORGAN SITE	SIDE EFFECT Mitoxantrone is typically well tolerated at standard doses.[3]
Clinically important side effects are in ***bold, italics***	
(arrhythmia)	ECG changes (11%)
cardiovascular (general)	***cardiomyopathy***
	CHF (2-5%); may occur during and months to years after treatment; deaths have occurred
	decreased left ventricular ejection fraction (≤13%); may occur during and months to years after treatment
	hypertension (4%)
	hypotension
	ischemia (5%)
	myocardial infarction
constitutional symptoms	diaphoresis (9%)
	fatigue (≤39%)
	fever (6-78%)
	weight changes (13-17%)
dermatology/skin	*extravasation hazard: irritant*[13]*;* rare cases of tissue necrosis have been reported; reversible blue discolouration of the skin has occurred with extravasation
	alopecia* (15-61%, severe 1%); typically mild; case reports of selective alopecia of white but not dark hair[8]
	bruising (6-11%)
	nail pigmentation
	onycholysis (11%)
gastrointestinal	*emetogenic potential: low to low- moderate*[14]
	anorexia (22-25%)
	constipation (10-16%)
	diarrhea* (4-47%)[5,8]
	dyspepsia (5-14%)
	nausea and vomiting* (10-35%, severe 4%)[3,8] typically mild and transient
	stomatitis/mucositis* (4-54%, severe <1%); typically occurs within 1 week of treatment[8]
	ulcers (10%)
hemorrhage	gastrointestinal bleed (2-16%)
	hemorrhage* (6%)
hepatobiliary/pancreas	hepatic toxicity* (<1%)[8]; severe impairment reported in leukemic patients
infection	infection* including urinary tract (7-32%), upper respiratory tract (7-53%), pneumonia (9%)
lymphatics	edema (10-31%)
metabolic/laboratory	hyperglycemia (10-31%); likely related to concurrent steroid administration[12]
	hyperuricemia
	hypocalcemia (10%)

ORGAN SITE	SIDE EFFECT Mitoxantrone is typically well tolerated at standard doses.[3]
Clinically important side effects are in ***bold, italics***	
	hypokalemia (7-10%)
	hyponatremia (9%)
	increased blood urea nitrogen (22%)
	increased liver enzymes (≤37%)[5,8]
	increased serum creatinine (13%)
	proteinuria (6%)
musculoskeletal	weakness (24%)
neurology	anxiety (5%)
	confusion
	depression (5%)
	drowsiness
	paraesthesia
	seizures (2-4%)
ocular/visual	blue discolouration of the sclera (<1%); reversible
	blurred vision (3%)
	conjunctivitis (5%)
pain	headache (6-13%)
	pain (8-41%); including abdominal pain (9-15%), back pain (8%), myalgia (5%), arthralgia (5%)
pulmonary	cough (5-13%)
	dyspnea (6-18%)
	rhinitis/sinusitis (5-6%)
renal/genitourinary	blue-green colouration of urine (6-11%); typically occurs for 24h after treatment
	hematuria (11%)
	renal toxicity (8%)
secondary malignancy	AML and MDS (~1-2%)
sexual/reproductive function	amenorrhea (28-53%), menstrual disorder (26-61%)
	impotence (7%)
	reduction in spermatogenesis; typically reversible[3,8,11]
syndromes	tumour lysis syndrome (<1%)

Adapted from standard reference[3,5] unless specified otherwise.

In leukemic patients, due to higher doses used, the side effects profile may differ; the following toxicities have been reported[5,7]:

- diarrhea, 9-13%
- increased incidence of bleeding and infection; sepsis, 31-34%
- moderate nausea or vomiting, 8%
- moderate or severe alopecia, 11 %

- moderate or severe stomatitis/mucositis, 9-29%
- moderate or severe jaundice or hepatitis, 8%

Cardiotoxicity is thought to be due to free radical damage as myocardial tissue is susceptible to these highly reactive species.[15] Anthracycline cardiotoxicity may present with early or late effects.[16,17] The following information applies to all anthracyclines, anthracenediones and mitoxantrone.[15,17,18]

Early cardiotoxic effects are not dose-related and may present from mild ECG changes to life-threatening arrhythmias.[15,16,18] These events may occur during or immediately after a single dose of anthracycline treatment,[15,18] but do not predict subsequent development of delayed cardiotoxicity and are not considered indications for suspension of therapy.[15,16,18-21]

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.[15,17-20] Abnormalities in LVEF are associated with all the anthracyclines and their derivatives.[17] LVEF changes are related to the total cumulative dose, are irreversible and refractory to medical therapy. [15,22]

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.[17] Late cardiotoxic effects may be prevented by stopping treatment with the associated anthracycline once patients have reached the suggested maximum cumulative dose.[15,22] Management of anthracycline cardiotoxicity includes discontinuation of the drug and initiating standard treatment of CHF.[17]

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).[17] Cardioprotectant therapy with dexrazoxane may be considered for patients with cumulative doxorubicin-equivalent doses greater than 300 mg/m^2.[18,23,24]

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**[25-27]*****	SUGGESTED **MONITORING THRESHOLD**[17,28-34]******
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[26]

** 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.

Hyperuricemia may result from cell lysis by mitoxantrone and may lead to electrolyte disturbances or acute renal failure.[35] 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[36]:

- 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.[37] 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.[38]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
quinolones (e.g., ciprofloxacin)[39]	delayed, moderate, possible; the antimicrobial effect of quinolones may be decreased	quinolone absorption decreased due to alteration of the intestinal mucosa	monitor for response to quinolone therapy, adjust quinolone dose as necessary

SUPPLY AND STORAGE:

Injection: Hospira Healthcare Corporation supplies mitoxantrone as a 2 mg/mL dark blue solution in 10 and 12.5 mL single-use vials. Store at room temperature; do not freeze. Protect from light.[3]

Novopharm Limited supplies mitoxantrone as a 2 mg/mL dark blue solution in 10 mL single-use vial. Store at room temperature; do not freeze. Protect from light.[7]

Pharmaceutical Partners of Canada supplies mitoxantrone as a 2 mg/mL dark blue solution in 10 mL single-use vial. Store at room temperature.[6] Product is not light-sensitive.[40]

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: should be diluted to at least 50 mL prior to use[3,6,7]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous[3]	not recommended
Intramuscular[3]	not recommended
Direct intravenous	not recommended; has been used[5,41-43]
Intermittent infusion[2,3]	***slowly*** (***over 3-5 minutes*****;** typically given over 15-30 minutes*) **into tubing of running IV***
Continuous infusion[1,5]	has been used
Intraperitoneal[3,8]	has been used
Intrapleural[44]	investigational

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

Intrathecal[3]	not recommended; neuropathy and neurotoxicity including paralysis, seizures, and bowel and bladder dysfunction have occurred
Intra-arterial[3]	not recommended; local/regional neuropathy which may be irreversible has been reported
Intravesical[45,46]	investigational

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*:**

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

Intravenous:	Cycle Length: ***3***-4 ***weeks***[2,3,5,10]:	***12***-14 *mg/m²* ***IV for one dose on day 1*** (total dose per cycle 12-14 mg/m²)
	induction[3]:	12 mg/m² IV once daily for 5 consecutive days starting on day 1 (total dose 60 mg/m²)
	induction and re-induction[2,3]:	10-12 mg/m² IV once daily for 2-3 consecutive days starting on day 1 (total dose per cycle 20-36 mg/m²)
	consolidation:[2,3]:	12 mg/m² IV once daily for 2 consecutive days starting on day 1 (total dose per cycle 24 mg/m²)
Suggested maximum cumulative dose[47-49]*:*	160 mg/m²	
Concurrent radiation:	has been used[50-53]	
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:	safety and effectiveness have not been established[3]; limited renal excretion, adjustment likely not required[2]	
Dosage in hepatic failure:	consider dosage adjustment[5]; no dosing details found, contraindicated in severe hepatic impairment[3]	
Dosage in dialysis:	extensive tissue binding; unlikely cleared by dialysis; supplemental dose not required[5,54]	

Children:

	Cycle Length:	
Intravenous:	safety and effectiveness have not been established[3]; has been used[1,3,55]	
	n/a[1,55]:	8-12 mg/m^2 IV once daily for 3-5 consecutive days starting on day 1 (total dose 24-60 mg/m^2)
	n/a[1]:	0.4 mg/kg/day IV once daily for 3-5 consecutive days starting on day 1 (total dose 1.2-2.0 mg/kg)
	n/a[1]:	12 mg/m^2 IV once daily for 2-3 consecutive days starting on day 1 (total dose 24-36 mg/m^2)
	3-4 weeks[1]:	18-20 mg/m^2 IV for one dose on day 1 (total dose per cycle 18-20 mg/m^2)

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