Drug Monograph

A - Drug Name

mitoXANTRONE

SYNONYM(S): DHAD; dihydroxyanthracenedione dihydrochloride; mitozantrone

COMMON TRADE NAME(S): Novantrone® (Brand Discontinued)

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B - Mechanism of Action and Pharmacokinetics

Mitoxantrone is an anthracenedione structurally similar to doxorubicin and daunorubicin. The exact mechanism of action is unknown but includes intercalation with DNA to cause inter/intrastrand cross-linking, inhibition of RNA synthesis and DNA topoisomerase II. Mitoxantrone is cell cycle phase-nonspecific.

Absorption	Oral absorption: Poor	
Distribution	Widely distributed into tissues.	
	Cross blood brain barrier?	minimal
	PPB	78 %
Metabolism	In liver to polar compounds, pathways not known.	
	Active metabolites	no
	Inactive metabolites	yes
Elimination	Triphasic. Mainly in bile (25% in feces within 5 days), small amount in urine.	
	Urine	11 % within 5 days, 65% unchanged.
	Half-life	23-215 hours (terminal t½)

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C - Indications and Status

Health Canada Approvals:

- Acute nonlymphocytic leukemia in adults (in combination), including myelogenous, promyelocytic, monocytic and erythroid acute leukemias
- Relapsed leukemia, lymphoma and hepatoma
- Metastatic breast cancer

Other Uses:

- Hormone refractory prostate cancer (with steroids)

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Vesicant

The following table contains adverse effects reported mainly in combination with corticosteroid in prostate cancer.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (7%) (transient)	I
	Cardiac ischemia (5%)	E
	Heart failure (2.6%)	D L
	Hypertension (4%)	E
	Hypotension	E
Dermatological	Alopecia (29%)	E
	Nail disorder (11%)	D
	Nail loss	D
Gastrointestinal	Abdominal pain	E

	Anorexia (25%)	E
	Constipation (16%)	E
	Dehydration (rare)	E
	Diarrhea (14%)	E
	Dyspepsia (5%)	E
	GI hemorrhage (rare)	E
	Mucositis (29%)	E
	Nausea (61%)	I
	Vomiting (9%)	I
	Weight changes (17%)	E
General	Edema (30%)	E
	Fatigue (39%)	E
	Fever (6%)	E
Hematological	Myelosuppression (nadir 10 days, recovery 21 days)	E
Hepatobiliary	↑ LFTs (20%)	E
Hypersensitivity	Anaphylaxis (rare)	I
Infection	Infection (10%)	E
Injection site	Phlebitis (10%)	I
	Vein discolouration (blue; rare)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (up to 10%)	E
	Tumor lysis syndrome (rare, in AML)	I
Musculoskeletal	Arthralgia (5%)	E
	Myalgia (5%)	E
Neoplastic	Leukemia (secondary) (1-2%)	L
	MDS (1-2%)	L
Nervous System	Anxiety (5%)	E
	Confusion (rare)	E
	Depression (5%)	E
	Headache (rare)	E
	Paresthesia (rare)	E
	Seizure (rare)	E
	Somnolence (rare)	E
Ophthalmic	Blurred vision (3%)	I E

	Conjunctivitis	I E
Renal	Creatinine increased (13%)	E
	Nephrotoxicity (occasional)	I E
	Proteinuria (6%)	I E
Reproductive and breast disorders	Irregular menstruation (amenorrhea)	D
Respiratory	Cough (5%)	E
	Dyspnea (15%)	E
	Pneumonitis (rare)	E D
Urinary	Urine discoloration (blue-green, 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.
Dose-limiting side effects are underlined.

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

Mitoxantrone may be associated with less nausea and vomiting, stomatitis and alopecia than doxorubicin.

Cardiotoxicity may occur with mitoxantrone for months to years after treatment, whether or not cardiac risk factors are present. It is cumulative across members of this class and anthracyclines. The recommended maximum cumulative dose of mitoxantrone is 140 mg/m^2. At this dose, 13% of patients have moderate to severe decreases in LVEF while 3% of patients may have clinical cardiac failure. The cumulative dose is lower with prior anthracycline therapy, in patients who have received radiation to the mediastinal area or concomitant therapy with other cardiotoxic agents such as cyclophosphamide, in children and in patients with active or dormant cardiovascular disease or multiple sclerosis.

Stomatitis is dose-limiting with the 5-day schedule and with the high doses used for bone marrow transplantation (e.g. high grade mucositis in nearly 70% of BMT patients in one study). It usually occurs within 1 week of therapy.

Signs and symptoms (e.g. hyperuricemia, hyperkalemia, hypocalcemia, acute renal failure, elevated LDH, high fever) consistent with **tumour lysis syndrome** have been reported to occur within 1 to 2 hours after first infusion. Patients at risk (high tumour burden) should be closely monitored and prophylaxis considered.

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E - Dosing

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 white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy. Except for the treatment of acute nonlymphocytic leukemia, mitoxantrone should not be given to patients with baseline neutrophil counts of less than 1.5 x 10^9/L.

Adults:

Solid tumours:

- q3w: 12-14 mg/m^2 IV
- Decrease by 2-4 mg/m^2 for combination therapy, prior therapy, or poor performance status

Leukemia:

- Single agent: 12 mg/m^2/day IV x 5 days
- With cytarabine: 10 – 12 mg/m^2 x 3 days. If a second course is indicated: 10-12 mg/m^2 x 2 days

Maximum lifetime dose:

- 140 mg/m^2 (no prior anthracycline, normal cardiac function; lower in children and patients with multiple sclerosis).
- Careful cardiac monitoring is important as cardiotoxicity may occasionally occur at lower cumulative doses. If tumour responding when lifetime dose reached, obtain cardiac consultation before continuing treatment.

Dosage with Toxicity:

Dosage in myelosuppression:

Modify according to protocol by which patient is being treated; if no guidelines available refer to Appendix 6 "Dosage Modification Hematologic and Non-Hematologic Toxicities".

Suggested modifications are:

WBC and Platelet Nadir ($x 10^9/L$)			Time to Recovery	Subsequent Dose
WBC		Platelets		
> 1.5	AND	> 50	≤ 21 days	No change. May increase by 2mg/m^2 if inadequate myelosuppression
			> 21 days	Hold until recovery. Do not increase dose
1 to 1.499	OR	25 to 49		Reduce dose by 2mg/m^2
< 1	OR	< 25		Reduce dose by 4mg/m^2

Dosage with Hepatic Impairment:

Hepatic Impairment	Dose
Mild-Moderate	↓ 50%
Bilirubin > 2-3 x ULN	Hold
Severe	Hold

Dosage with Renal Impairment:

No adjustment required

Dosage in the elderly:

May have an increased risk of toxicity

Children:

Safety and efficacy not established

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F - Administration Guidelines

- Doses may be mixed in 50-100mL minibag (Normal Saline or 5% Dextrose); Infuse through sidearm of free flowing IV over 10-30 minutes.
- Slow push through sidearm of free-flowing IV, not less than 3 to 5 minutes.
- Mitoxantrone should not be mixed in the same infusion with heparin since a precipitate may form.
- Do not admix with other drugs.
- 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.
- Store at room temperature.

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G - Special Precautions

Other:

Mitoxantrone is **contraindicated** in patients with known hypersensitivity to mitoxantrone, its excipients or other anthracyclines. Mitoxantrone should not be used for intrathecal, subcutaneous, intramuscular or intra-arterial administration. Vaccination with live vaccines is contraindicated. It is also contraindicated in patients with severe hepatic impairment, in patients who have not recovered from severe myelosuppression due to prior cytotoxic or radiation treatment, and in patients with abnormal cardiac function who have received prior substantial anthracycline exposure. Mitoxantrone should be used with caution in patients with poor performance status.

Cardiotoxicity is cumulative across members of the anthracycline (daunorubicin, doxorubicin, epirubicin, idarubicin) and anthracenedione (mitoxantrone) classes of drugs. Patients who have received these drugs are at increased risk of toxicity and should be carefully monitored. The safe cumulative dose is lower in patients who have received radiation to the mediastinal area or concomitant therapy with other cardiotoxic agents such as cyclophosphamide.

Mitoxantrone is **mutagenic, clastogenic, carcinogenic and fetotoxic** and should not be used in **pregnancy**. Adequate contraception should be used by both sexes, during mitoxantrone treatment and for at least 6 months after the last dose. Its effects on **fertility** have not been established. **Breast feeding** is not recommended due to secretion into breast milk.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cardiotoxic drugs (i.e., cyclophosphamide, trastuzumab, other anthracyclines)	↑ cardiotoxicity	Additive	Caution if prior treatment with these agents
Live vaccines	↑ risk of severe infection	Immunocompromised status	Avoid

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and regular
Serum uric acid levels (hematologic malignancies)	Baseline and regular
Cardiac function tests (Echo, RNA and/or MUGA scans) especially patients with risk factors, or close to the lifetime threshold	Baseline and regular
Liver function tests (especially If poor Performance Status)	Baseline and regular
Clinical assessment for symptoms of CHF, bleeding, infection, local toxicity.	At each visit

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

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K - References

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 1179-84.

Mitoxantrone: e-Cancer Chemotherapy Manual.

Prescribing Information: Novantrone® (mitoxantrone). OSI Pharmaceuticals, September 2009.

Product Monograph: Mitoxantrone Injection. Pharmaceutical Partners of Canada Inc., January 15, 2008.

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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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