Mitoxantrone

Class: Anthracenedione

Indications:

_Initial treatment of acute nonlymphocyticleukemias (ANLL [includes myelogenous, promyelocytic, monocytic and erythroidleukemias])

_treatment of advanced hormone-refractory prostate cancer

_secondary progressive or relapsing-remitting multiple sclerosis (MS)

_prostate caner (unlabeled)

_breast cancer(unlabeled)

_Hodgkin lymphoma (unlabeled)

_non- Hodgkin lymphoma(unlabeled)

Available dosage form in the hospital:20 MG/10 ML VIAL

Trade name : Novantrone

Doses: Details concerning dosing in combination regimens should also be consulted.

U.S. labeling:

-Acute nonlymphocyticleukemias (ANLL):

-*Acute myeloid leukemia (AML) induction:* 12 mg/m^2 once daily for 3 days (in combination with cytarabine); for incomplete response, may repeat (7-10 days later) at 12 mg/m^2 once daily for 2 days (in combination with cytarabine) (Arlin, 1990)

-*AML consolidation* (beginning ~6 weeks after initiation of the final induction course): 12 mg/m^2 once daily for 2 days (in combination with cytarabine), repeat in 4 weeks (Arlin, 1990)

-Multiple sclerosis: 12 mg/m^2 every 3 months (maximum lifetime cumulative dose: 140 mg/m^2; discontinue use with LVEF <50% or clinically significant reduction in LVEF)

-Prostate cancer (advanced, hormone-refractory): 12-14 mg/m^2 every 3 weeks (in combination with corticosteroids)

Canadian labeling:

-Acute nonlymphocyticleukemias (ANLL):

-*AML induction:* 10-12 mg/m^2 once daily for 3 days (in combination with cytarabine); for incomplete response, may repeat at 10-12 mg/m^2 once daily for 2 days (in combination with cytarabine)

-*AML consolidation* (beginning ~6 weeks after initiation of the final induction course): 12 mg/m^2 once daily for 2 days (in combination with cytarabine), repeat in 4 weeks

-**Acute leukemias (relapsed):** Induction: 12 mg/m^2 once daily for 5 consecutive days; may repeat once if needed (at the same dose and duration)

-**Breast cancer (metastatic), lymphoma:** Initial: Single agent: 14 mg/m^2 every 21 days; reduce initial dose to ≤12 mg/m^2 for myelosuppression due to previous treatment or for poor general health. When used in combination with other agents, reduce initial dose to 10-12 mg/m^2.

-**Hepatocellular cancer:** Initial: Single agent: 14 mg/m^2 every 21 days; reduce initial dose to ≤12 mg/m^2 for myelosuppression due to previous treatment or for poor general health

***Adult unlabeled uses and/or dosing:*

-**AML, refractory:**

-*CLAG-M regimen:* 10 mg/m^2 once daily for 3 days (in combination with cladribine, cytarabine, and filgrastim), may repeat once if needed

-*MEC or EMA regimen:* 6 mg/m^2 once daily for 6 days (in combination with cytarabine and etoposide)

-*Mitoxantrone/Etoposide:* 10 mg/m^2 once daily for 5 days (in combination with etoposide)

-**APL consolidation phase (second course):** 10 mg/m^2 once daily for 5 days

-**Hodgkin lymphoma, refractory:**

-*MINE-ESHAP regimen:* 10 mg/m^2 on day 1 every 28 days for up to 2 cycles (MINE is combination with mesna, ifosfamide, mitoxantrone, and etoposide; MINE alternates with ESHAP for up to 2 cycles of each)

-*VIM-D regimen:* 10 mg/m^2 on day 1 every 28 days (in combination with etoposide, ifosfamide, mesna, and dexamethasone)

-**Non-Hodgkin lymphoma (as part of combination chemotherapy regimens):**

- *CNOP regimen:* 10 mg/m^2 every 21 days
- *FCMR regimen:* 8 mg/m^2 every 28 days
- *FMR regimen:* 10 mg/m^2 every 21 days
- *FND regimen:* 10 mg/m^2 every 28 days
- *MINE-ESHAP regimen:* 8 mg/m^2 every 21 days for 6 cycles (MINE is combination with mesna, ifosfamide, mitoxantrone, and etoposide; followed by ESHAP)

-**Stem cell transplantation, autologous:** 60 mg/m^2 administered 4-5 days prior to autografting (as 3 divided doses over 1 hour each at 1-2 hour intervals on the same day; in combination with other chemotherapeutic agent[s]).

Geriatric
Refer to adult dosing.

Renal Impairment:

- No dosage adjustment provided in manufacturer's labeling (has not been studied).
- Hemodialysis: Supplemental dose is not necessary
- Peritoneal dialysis: Supplemental dose is not necessary
- Elderly: Clearance is decreased in elderly patients; use with caution

Hepatic Impairment:

-***U.S. labeling:*** No dosage adjustment provided in the manufacturer's labeling; however, clearance is reduced in hepatic dysfunction. Patients with severe hepatic dysfunction (bilirubin >3.4 mg/dL) have an AUC of 3 times greater than patients with normal hepatic function; consider dose adjustments. **Note:** MS patients with hepatic impairment should not receive mitoxantrone.

-***Canadian labeling:***

-Mild-to-moderate impairment: No specific dosage adjustment provided; consider dose adjustments and monitor closely.

-Severe impairment: Use is contraindicated.

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

-ANLL patients: Severe or life-threatening nonhematologic toxicity: Withhold treatment until toxicity resolves

-MS patients:

- Neutrophils <1500/mm^3: Use is not recommended.
- Signs/symptoms of HF: Evaluate for cardiac signs/symptoms and LVEF.
- LVEF <50% or baseline LVEF below the lower limit of normal (LLN): Use is not recommended.

***Canadian labeling (not in U.S. labeling):* Hepatocellular cancer, lymphoma, or breast cancer (metastatic):**

- WBC nadir >1500/mm^3 **and** platelet nadir >50,000/mm^3 and recovery ≤21 days: Repeat previous dose or increase dose by 2 mg/m^2 if myelosuppression is inadequate.
- WBC nadir >1500/mm^3 **and** platelet nadir >50,000/mm^3 and recovery >21 days: Withhold treatment until recovery then resume at previous dose.
- WBC nadir <1500/mm^3 **or** platelet nadir <50,000/mm^3 (regardless of recovery time): Withhold treatment until recovery then decrease previous dose by 2 mg/m^2.
- WBC nadir <1000/mm^3 **or** platelet nadir <25,000/mm^3 (regardless of recovery time): Withhold treatment until recovery then decrease previous dose by 4 mg/m^2.

Common side effect :

>10%:

Cardiovascular: Edema (10% to 30%), arrhythmia (3% to 18%), cardiac function changes (≤18%), ECG changes (≤11%)

Central nervous system: Fever (6% to 78%), pain (8% to 41%), fatigue (≤39%), headache (6% to 13%)

Dermatologic: Alopecia (20% to 61%), nail bed changes (≤11%), petechiae/bruising (6% to 11%)

Endocrine & metabolic: Menstrual disorder (26% to 61%), amenorrhea (28% to 53%), hyperglycemia (10% to 31%)

Gastrointestinal: Nausea (26% to 76%), vomiting (6% to 72%), diarrhea (14% to 47%), mucositis (10% to 29%; onset: ≤1 week), stomatitis (8% to 29%; onset: ≤1 week), anorexia (22% to 25%), weight gain/loss (13% to 17%), constipation (10% to 16%), GI bleeding (2% to 16%), abdominal pain (9% to 15%), dyspepsia (5% to 14%)

Genitourinary: Urinary tract infection (7% to 32%), abnormal urine (5% to 11%)

Hematologic: Neutropenia (79% to 100%; onset: ≤3 weeks; grade 4: 23% to 54%), leukopenia (9% to 100%), lymphopenia (72% to 95%), anemia/hemoglobin decreased (5% to 75%) thrombocytopenia (33% to 39%; grades 3/4: 3% to 4%), neutropenic fever (≤11%)

Hepatic: Alkaline phosphatase increased (≤37%), transaminases increased (5% to 20%), GGT increased (3% to 15%)

Neuromuscular & skeletal: Weakness (≤24%)

Renal: BUN increased (≤22%), creatinine increased (≤13%), hematuria (≤11%)

Respiratory: Upper respiratory tract infection (7% to 53%), pharyngitis (≤19%), dyspnea (6% to 18%), cough (5% to 13%)

Pregnancy category : D