Drug Monograph

A - Drug Name

mitomycin

SYNONYM(S): mitomycin C; MMC

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

back to top

B - Mechanism of Action and Pharmacokinetics

Mitomycin is a purple antibiotic isolated from Streptomyces caespitosus. Mitomycin is activated in vivo to a bifunctional and trifunctional alkylating agent. Binding to DNA leads to cross-linking and inhibition of DNA synthesis and function. RNA synthesis is also inhibited at higher mitomycin concentrations. Mitomycin is cell cycle phase-nonspecific.

Absorption	Oral absorption: Erratic	
	Not appreciably absorbed from the bladder	
Distribution	Rapidly cleared from plasma. Highest concentraions found in kidney, followed by muscles, eyes, lungs, intestine and stomach. Found in ascites.	
	Cross blood brain barrier?	no
	PPB	No information found
Metabolism	Prodrug activated in vivo, primary means of elimination is by hepatic metabolism, also metabolized by enzymes in kidneys, spleen, brain and heart; saturable at relatively low doses.	
	Active metabolites	yes

	Inactive metabolites	yes
Elimination	Biphasic elimination. Excreted in urine, detected in bile and feces, biliary level may exceed plasma level.	
	Urine	10% excreted unchanged in urine, increases with increasing doses.
	Half-life	17 minutes

back to top

C - Indications and Status

Health Canada Approvals:

Topical

- Transitional cell bladder cancer (superficial), 1st or 2nd line

Systemic

- Stomach cancer (palliative)
- Colon cancer (palliative)

Other Uses:

- Anal cancer
- Vulvar cancer

back to top

D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Vesicant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (rare, with prior anthracyclines)	E D

	Venous thromboembolism	E
Dermatological	Alopecia (frequent)	E
	Radiation recall reaction (rare)	I
	Rash (10%, generally on extremities)	I E
Gastrointestinal	Anorexia	E
	Diarrhea	E
	Mucositis (4%)	E
	Nausea, vomiting	I
General	Edema	E
	Fatigue	E
	Pain	E
Hematological	Hemolytic uremic syndrome (rare)	D
	Myelosuppression ± infection, bleeding (64%)	E
Injection site	Injection site reaction (may be severe)	I
Metabolic / Endocrine	Hypoglycemia	E
Nervous System	Ataxia	E
Renal	Nephrotoxicity (2%) (may be severe)	D
Reproductive and breast disorders	Irregular menstruation (amenorrhea)	E
Respiratory	Adult respiratory distress syndrome (ARDS) (or other acute respiratory symptoms; especially with vincas)	E
	Pneumonitis	E D
Urinary	Bladder fibrosis (with intravesical use)	I E D
	Cystitis (25%) (with intravesical use)	I E D

* "*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)

Cumulative ***myelosuppression*** is a major dose-limiting adverse effect. Onset and recovery may be late (2-4 weeks and 10 weeks respectively). .

The ***tissue necrosis*** that happens with ***extravasation*** may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected. Soft tissue ulceration distal to the injection site following uneventful injection in a peripheral vein has been reported.

Pulmonary toxicity consisting of dyspnea, non-productive cough or pulmonary infiltrates has been reported infrequently, and may be severe, with both single agent and combination chemotherapy. Threshold dose associated with pulmonary toxicity appears to be 50-60 mg/m^2. Steroids may be of some benefit. Acute respiratory distress syndrome may occur with high FIO_2 concentrations and combination chemotherapy.

A syndrome of ***renal failure and microangiopathic hemolytic anemia*** (***hemolytic-uremic syndrome***) with hypertension, pulmonary edema and neurological symptoms has been reported in 10% of patients. This syndrome mostly appears after 6 months of therapy/ 60mg of mitomycin, and may be exacerbated with blood transfusions. Patients should be monitored for development of renal failure or hemolysis.

The incidence of ***cardiotoxicity*** may be increased in patients receiving mitomycin in combination with doxorubicin or in patients who have had prior exposure to doxorubicin. No studies report cardiotoxicity in patients only receiving mitomycin.

Genitourinary irritation, following intravesical (bladder) administration includes dysuria, cystitis, nocturia, increased micturition and hematuria. Myelosuppression has not been noted with intravesical administration. Bladder fibrosis/contraction or calcification have rarely been reported.

Mitomycin has the potential to enhance radiation injury to tissues. While often called ***radiation recall reactions***, the timing of the radiation may be before, concurrent with or even after the administration of the mitomycin. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

back to top

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. Patients should not be retreated until hematological recovery has occurred.

Adults:

Intravenous:

- On days 1 and 29: 10 mg/m^2
- Q6-8W: 20 mg/m^2
- q6-8w: 2 mg/m^2/day x 5 days, stop x 2 days, repeat x 1 (i.e. day 1-5 and day 8-12)

Intravesical:

- q1w: 20-40 mg in SWI x 8 weeks

Dosage with Toxicity:

Dosage in myelosuppression: Modify according to protocol by which patient is being treated.

Lowest Value in Preceding Course		
ANC ($x10^9$/L)	Platelets ($x\ 10^9$/L)	% Previous dose*
≥ 1	≥ 75	100
0.5 - 0.99	25-74.99	70
< 0.5	< 25	50 or discontinue

*Do not re-treat until platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L and other toxicities ≤ grade 2.

Other Toxicity:

Toxicity	Mitomycin dose
Pneumonitis	Hold and investigate if suspected. Discontinue if confirmed. Consider steroids.
Hemolytic uremic syndrome	Discontinue
Grade 3 organ/non-hematologic	Hold until ≤ grade 2 and then reduce by 25%
Grade 4 organ/non-hematologic	Discontinue

Dosage with Hepatic Impairment:

No adjustment required

Dosage with Renal Impairment:

Do not administer if creatinine > 150 µmol/L, or in patients with moderate to severe renal impairment.

Dosage in the elderly:

Has not been studied, but caution recommended due to likelihood of organ dysfunction.

Children:

Safety and efficacy have not been established.

back to top

F - Administration Guidelines

- Slow push through sidearm of free flowing IV (Normal Saline)
- Doses may be mixed in 50mL minibag (Normal Saline); Infuse through a free-flowing IV over 15-30 minutes

back to top

G - Special Precautions

Other:

Mitomycin is **contraindicated** in patients with serious infections, myelosuppression, coagulation disorder, or an increased bleeding tendency due to other causes, with known hypersensitivity or an idiosyncratic reaction to it, or any component of its formulations, even if intended for intravesical use.

High FIO_2 concentrations (anesthesia, oxygen therapy) should be avoided especially in patients with pulmonary toxicity.

Mitomycin has been shown to be **carcinogenic, fetotoxic, mutagenic, clastogenic** and **teratogenic** in animal studies and should not be used in **pregnancy**. Adequate contraception must be used by both sexes, during mitomycin treatment and for at least 6 months after the last dose. **Breast feeding** is not recommended due to the potential secretion into breast milk. **Fertility** may be affected.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
vinca alkaloids (vincristine, vinblastine, vindesine)	acute bronchospasm occurring within minutes or hours after vinca alkaloid injection	Unknown	Caution

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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and regular
Renal function tests	Baseline and periodic
Clinical exam, including pulmonary, neurological, infection, bleeding, thromboembolism, GI effects and local site toxicity	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and regular
Fluid balance, in patients experiencing pulmonary toxicity	

back to top

K - References

BCCA Protocol Summary for the Chemotherapy of Pseudomyxoma Peritonei using intraperitoneal Mitomycin and Fluorouracil. Accessed September 10, 2012.

McEvoy GK, editor. AHFS Drug Information 2011. Bethesda: American Society of Health-System Pharmacists, p. 1159-61.

Product Monograph: Mitomycin. Hospira Healthcare Corporation. June 13, 2007.

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Mitomycin: UpToDate® drug information (v19.2). Accessed September 10, 2012.

August 2016 edited indications

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