ANTITUMOR ANTIBIOTICS

ANTHRACYCLINES

DOXORUBICIN
(ADRIAMYCIN PFS®, RUBEX®, ADRIAMYCIN RDF®)
DAUNORUBICIN
(CERUBIDINE®)
IDARUBICIN
(IDAMYCIN®, IDAMYCIN PDF®)
EPIRUBICIN
(ELLENCE®)

ANTHRACENEDIONES

MITOXANTRONE
(NOVANTRONE®)
PIXANTRONE*
(*NOT AVAIL; FDA FAST TRACK 7/04)

DOXORUBICIN/DAUNORUBICIN/IDARUBICIN/EPIRUBICIN

I. MECHANISM OF ACTION

A) These four drugs diffuse freely across cell membranes and into the cell nucleus.
B) Once inside, they intercalate with DNA, which means they physically enter the double helix and interfere with uncoiling.
C) More importantly, the drugs interfere with topoisomerase II, an enzyme that promotes strand breakage and resealing. Topoisomerase II is one of the enzymes that repair DNA. Apparently, intercalation alters the shape of DNA such that topoisomerase II cannot repair damaged DNA.
D) When topoisomerase II, DNA and an anthracycline are bound together, DNA strand breaks appear.
E) In addition, doxorubicin, daunorubicin and epirubicin cause formation of free radicals, chemicals with one too many electrons, which chemically damage cell structures. Free radical formation involves water or iron. Free radical formation most certainly contributes to the cardiotoxicity of these drugs and possibly to their antineoplastic activity. The heart lacks a good defense system against free radicals along with rapid production of hydrogen peroxide, both of which make the heart very sensitive to the anthracyclines.
F) Resistance is due to P-glycoprotein, alteration of topoisomerase function or decreased topoisomerase concentration.

II. PHARMACOKINETICS

A) Idarubicin has an oral bioavailability of 30%. More of the active metabolite, idarubicinol, is formed by the oral route than the IV route. Idarubicinol is an active metabolite and is equi- or more potent than the parent compound.
B) Distribution- Enters cells rapidly. Does not cross into the CSF in appreciable amounts.
C) Metabolism- A small fraction of doxorubicin is metabolized in the liver, but it mostly circulates as unchanged drug. Daunorubicin undergoes more extensive metabolism. Metabolites of both drugs are inactive. Idarubicin is extensively metabolized to idarubicinol, which is equally as potent as the parent. Epirubicin is extensively metabolized to epirubicinol, which has one-tenth the cytotoxic activity of epirubicin.
D) Elimination- 10% is eliminated in the urine, 50% is eliminated in the bile. It takes 30 - 50 hours to remove 70% of the drug. Dosage adjustments should be made for hepatic impairment (see table in Dosage and Administration).

III. DOSAGE AND ADMINISTRATION

A) These drugs can be given IV push into a running IV line in a peripheral site, but the IV site should be well placed and secure since all four are vesicants.
B) Administration through central venous access can be done via a short or continuous infusion over hours to days.
C) How these drugs are administered does not affect antineoplastic activity, but does alter toxicity. Activity is related to AUC not peak.
D) Cardiotoxicity is related to high peak concentrations so that IV push leads to a higher incidence of cardiotoxicity than does continuous infusion.
E) Nausea and vomiting are more common with IV push.
F) Mucositis is more common with continuous infusions.
G) Doxorubicin has also been instilled into the urinary bladder and into pleural effusions.
H) Doxorubicin is incompatible with heparin, 5-FU, and methotrexate, but compatible with DTIC, vincristine, vinblastine, and cyclophosphamide.
I) Doxorubicin and daunorubicin are now available in liposomal dosage forms called Doxil® and DaunoXome®, respectively. These should not be interchanged with the original products. The dosing is distinctly different.

DRUG	ADJUSTMENT FOR HEPATIC DYSFUNCTION (% OF THE NORMAL DOSE THAT SHOULD BE ADMINISTERED)						
	Tbili < 1.5	SGOT < 60	Tbili 1.5-3.0	SGOT 60-180	Tbili 3.1-5	SGOT >180	Tbili >5
DOXORUBICIN*	100%		50%		25%		Omit
DAUNORUBICIN*	100%		75%		50%		Omit
MITOXANTRONE**	100%		50%		25%		Omit
IDARUBICIN**					Tbili 2.5 - 5 50%		Omit

References: * King PD, Perry MC. Hepatotoxicity of Chemotherapeutic Agents. In: The Chemotherapy Sourcebook, 3rd Edition. Lippincott Williams and Wilkins 2001; King PD, et al. Oncologist 2001;6:162 - 76; **Clinical Pharmacology Online, Accessed 3/30/05.

IV. TOXICITY

A) Myelosuppression - Onset in 7 - 20 days, nadir at day 16, recovery by day 24. This is more common and profound with daunorubicin.
B) Mucositis - onset in 7 - 10 days with rapid recovery. This is less common with daunorubicin. Less common with IV bolus administration.
C) Vesicant- Extravasation of idarubicin, doxorubicin, daunorubicin, or epirubicin can lead to extensive necrosis over days, weeks, or months. Treatment should include stopping administration, leaving the needle in place, removing as much fluid as possible, administering ice, taking photographs, contacting an oncologist, and requesting a plastic surgery consult.
D) Cardiotoxicity- More common in children than adults. Occurs because the heart lacks catalase and is losing glutathione peroxidase. It can take two forms, acute and chronic.
   Acute- a) Transient EKG changes occur commonly and have no clinical meaning. Common changes include ST and T wave changes, a prolonged QT interval, decreased QRS voltage, or frank atrial or ventricular arrhythmias: 10-25% of patients. Occurs within hours and is transient and are not dose dependent

or schedule dependent. If EKG changes occur, it is not an indication to change treatments.
b) Pericarditis/myocarditis characterized by fever, chest pain, and possibly CHF. It is idiosyncratic and rare.

Chronic-

a) Specific damage to myocardial tissue eventually leads to CHF. It occurs with each dose of idarubicin, doxorubicin, daunorubicin or epirubicin. The tissue damage is distinctly different from viral cardiomyopathy or ischemic injury.
b) The symptoms are similar to heart failure due to any other cause.
c) The incidence rises with cumulative doses. Up to 350 mg/m^2 of doxorubicin or daunorubicin or 700 mg/m^2 for epirubicin, the incidence is minimal. The risk rises above 1% for cumulative doses of 550 mg/m^2 of doxorubicin and daunorubicin. Doses greater than 900 mg/m^2 of epirubicin should be exceeded with caution. The lifetime dose for idarubicin has not been determined.
d) The onset can occur weeks to months after administration; can be as late as seven years after therapy.
e) The diagnosis of anthracycline cardiomyopathy requires a good H + P, MUGA, and a myocardial biopsy.
f) Management includes bed rest and afterload reduction. Digoxin is of little benefit in most cases.
g) The mortality rate is 30-50%.
h) Risk factors of cardiomyopathy: increasing cumulative dose, prior mediastinal irradiation exposure, and exposure to cyclophosphamide, vincristine, mitomycin C, mithramycin, actinomycin D, and bleomycin; schedule of administration; age; concomitant chemotherapy; prior history of cardiac disease.

Clinical Manifestations: sinus tachycardia; tachypnea; cardiomegaly; peripheral and pulmonary edema; venous congestion, pleural effusion.

Mechanism: injures myocytes by overloading them with calcium – mechanism unclear; free radical production by depleting glutathione, which is believed to protect cells from oxidative stress and free radical injury (by reducing peroxides to alcohols). Free radicals generated then damage membranes or macromolecules and produce cardiac dysfunction.

A clinical dilemma is what to do when the lifetime cumulative dose has been achieved yet the tumor is still present and responsive. Clinicians need to counsel patients in regards to the risk of tumor progression as well as cardiotoxicity.

Prevention-

a) Minimize the lifetime cumulative dose.
b) ↓ BP and avoid anthracyclines in pt with underlying cardiac disease.
c) Radiation to the chest may increase the risk of CHF such that after 20 Gy to the chest the lifetime cumulative dose of doxorubicin is often capped at 450 mg/m^2.
d) Use continuous infusions whenever possible.
e) Obtain serial MUGA's-controversial.
f) Reduce the dose in cases of elevated bilirubin.

g) Dexrazoxane–chemically similar to EDTA. Chelates iron in the heart, which is necessary for free radical formation. Only FDA approved when the cumulative dose of doxorubicin has reached 300 mg/m^2. Dosed at 10 times the doxorubicin dose. Give over 15 min and then administer doxorubicin within 30 min of the start of dexrazoxane.

E) Emesis – Nausea and vomiting occur within 4–8 hours and may last for 24 hours.
F) Radiation recall – Patients Rx an anthracycline + radiation therapy may develop a severe burn at the site of radiation.
G) Alopecia – Onset in 3 weeks but hair growth restarts 3 weeks after the last dose.

V. CLINICAL MONITORING

A) Labs– CBC with differential and platelets, bilirubin.
B) MUGA.
C) Physical exam– special attention to the cardiac, mucosal, dermatological, and urinary tract aspects of the exam.
D) Historical data– Cumulative lifetime dose (see table below), cardiac history, DXRT history
E) Counsel the patient about cardiac risk, alopecia, skin and nail changes, and orange discoloration of the urine.
F) Always be ready for an extravasation.

DRUG	LIFETIME DOSE
Doxorubicin	500 – 550 mg/m^2
Daunorubicin	500 – 600 mg/m^2
Doxorubicin + Cyclophosphamide	450 mg/m^2
Doxorubicin + Radiation	450 mg/m^2
Epirubicin	830 – 920 mg/m^2
Epirubicin + Cyclophosphamide	750 mg/m^2
Epirubicin + Radiation	750 mg/m^2
Idarubicin	Unknown, thought to be 120 mg/m^2
Mitoxantrone – Anthracycline naïve – Prior anthracyclines	 160 mg/m^2 120 mg/m^2

Conversion factors for anthracyclines (Keefe DL. Anthracycline-induced cardiomyopathy. *Semin Oncol* 2001;28(4 Suppl 12):2 – 7):

Doxorubicin = 1 (5% cardiotoxicity at 450 mg/m^2)
Daunorubicin = 0.5 (5% cardiotoxicity at 900 mg/m^2)
Epirubicin = 0.5 (5% cardiotoxicity at 935 mg/m^2)
Idarubicin = 2 (5% cardiotoxicity at 225 mg/m^2)
Mitoxantrone = 2.2 (5% cardiotoxicity at 200 mg/m^2)

Guidelines for monitoring patients receiving doxorubicin:

Perform baseline MUGA/echo at rest for calculation of LVEF prior to administration of 100 mg/m^2 of doxorubicin. Subsequent studies should be performed at least 3 weeks after the indicated total cumulative doses have been given, before consideration of the next dose.

Patients with a normal baseline LVEF (≥ 50%):

- Perform the 2nd study after 250 – 300 mg/m^2.
- Repeat study after 400 mg/m^2 in pts with known heart disease, radiation exposure, abnormal EKG results, or cyclophosphamide therapy; or after 450 mg/m^2 in the absence of any of these risk factors.
- Perform sequential studies thereafter prior to each dose.
- DC doxorubicin therapy once functional criteria for cardiotoxicity develop i.e. absolute decrease in LVEF ≥ 10% associated with a decline to a level ≤ 50%.

Patients with abnormal baseline LVEF (< 50%):

- Doxorubicin therapy should not be initiated with a baseline LVEF ≤ 30%.
- In patients with LVEF greater than 30% and less than 50%, sequential studies should be obtained prior to each dose.
- Discontinue doxorubicin with cardiotoxicity: absolute decrease in LVEF ≥ 10% and or final LVEF ≤ 30%.

DOXORUBICIN HCL LIPOSOME
(DOXIL®)

I. MECHANISM OF ACTION

Liposomal doxorubicin (Doxil®) is doxorubicin HCl encapsulated in STEALTH® liposomes for intravenous administration. The STEALTH® liposomes of Doxil® are formulated with surface-bound methoxypolyethylene glycol, a process often referred to as pegylation, to protect lipsomes from detection by the mononuclear phagocyte system and to increase blood circulation time.

II. PHARMACOKINETICS

A) Supplied in vials of 20mg (2 mg/mL).
B) The small steady state volume of distribution of liposomal doxorubicin shows that it is confined mostly to the vascular fluid volume. Plasma protein binding of liposomal doxorubicin has not been determined; the plasma protein binding of doxorubicin is approximately 70%. Because of the slower clearance of liposomal doxorubicin, the AUC is approximately 2 - 3 times larger than the AUC for a similar dose of conventional doxorubicin.
C) It is recommended that liposomal doxorubicin dosage be reduced if the bilirubin is elevated as follows: Serum bilirubin 1.2 to 3 mg/dL reduce the dose by 50%; if bilirubin 3 - 5 mg/dL reduce the normal dose by 25%; if bilirubin greater than 5 mg/dL OMIT dose.

III. DOSAGE AND ADMINISTRATION:

Ovarian cancer (50 mg/m^2 at an initial rate of 1 mg/min once every four weeks. In Kaposi's sarcoma it is administered at 20 mg/m^2 over 30 minutes once every three weeks.

Dose modification for hand-foot syndrome:

TOXICITY GRADE	DOSE ADJUSTMENT
1 (mild erythema, swelling or desquamation not interfering with daily activities)	Re-dose unless patient has experiences previous Grade 3/4 toxicity. If so, delay up to 2 weeks and ↓ dose by 25%. Return to original dose level.
2 (erythema, desquamation or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations < 2 cm)	Delay dosing up to 2 weeks or until resolved to Grade 0 -1. If after 2 weeks there is no resolution, DC liposomal doxorubicin. If resolved to Grade 0 -1 within 2 weeks, and there are no prior Grade 3/4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3/4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	Delay dosing up to 2 weeks or until resolved to Grade 0 - 1. ↓ Dose by 25% and return to original dose Interval. If after 2 weeks there is no resolution, DC liposomal doxorubicin.
4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	Delay dosing up to 2 weeks or until resolved to Grade 0 - 1. ↓ Dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, DC lipisomal doxorubicin.

DC = discontinue. Reference: Package Insert.

IV. TOXICITY

A) Experience with large cumulative doses of liposomal doxorubicin is limited. Liposomal doxorubicin's cardiac risk and its risk compared to conventional doxorubicin formulations have not been adequately evaluated.
B) Acute infusion related reactions – flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest and throat and/or hypotension have occurred in 5 to 10% of patients.
C) Liposomal doxorubicin is not a vesicant, but should be considered an irritant and precautions should be taken to avoid extravasation.
D) Others – palmar-plantar erythrodysesthesia (PPE) also known as hand-foot syndrome; radiation recall.

V. MONITORING

A) All patients being treated with liposomal anthracyclines should have a baseline MUGA scan. To reduce the risk of developing cardiotoxicity, liposomal anthracycline therapy should be cautiously used in patients with a LVEF < 50% at BL. Repeat MUGA scans should be performed after the cumulative dose reaches 400 mg/m^2 and again at every 100 -120 mg/m^2 cumulative dose increase thereafter.
B) Patients with a history of anthracycline treatment should have MUGA scans performed more frequently (e.g., after every 200 mg/m^2 dose increment).
C) If clinical signs of toxicity appear, then treatment should be stopped immediately.

Reference: Theodoulou M, Hudis C. *Cancer* 2004;100:2052 – 63.

MITOXANTRONE
(NOVANTRONE®)

I. MECHANISM OF ACTION - Blocks topoisomerase II activity just like doxorubicin but does not cause free radical formation.

II. PHARMACOKINETICS-

Rapid distribution throughout the body and remains in the body for weeks. Undergoes slow metabolism. 10% of a dose appears in the urine and 20% in the stool. Dosage adjustment in renal dysfunction is not necessary and for liver dysfunction it has not been specified.

III. DOSAGE AND ADMINISTRATION -

Given as a 30-minute infusion. Not classified as a vesicant.

Evidence against mitoxantrone being a vesicant:

A) The FDA-approved package insert does not state that it is a vesicant but does state that RARE reports of tissue necrosis have been reported.
B) Rare reports of necrosis are known for cisplatin and etoposide, yet they are both given regularly into peripheral IVs. KCL solutions can also cause necrosis upon extravasation.
C) The reports of necrosis in the mitoxantrone literature are confounded by concurrent administration of other vesicants.
D) Immunex has only nine reports on hand of skin necrosis since widespread use of mitoxantrone began in the 1980s.
E) Lederle, the original manufacturer, was sued on numerous occasions for failure to warn that mitoxantrone is a vesicant and has never lost.
F) The Oncology Nursing Society lists mitoxantrone as a non-vesicant.
G) The oncology nurses at Shands have given dozens of peripheral infusions of mitoxantrone, yet there is no recall of any necrosis ever occurring due to an extravasation.

IV. TOXICITY

A) The risk of cardiotoxicity is much less because the lifetime cumulative dose needed to cause such an effect is rarely achieved in the clinical setting. Overall, about 1.3% of patients have developed cardiotoxicity. The risk rises to 10% at a cumulative dose of 120 mg/m^2.
B) Mild nausea and vomiting in 52%.
C) Minimal alopecia in 23%.
D) Leukopenia- onset in 10-14 days and resolved by day 24.
E) Bluish discoloration of sclera, fingernails, or urine.

V. CLINICAL MONITORING

A) Labs- CBC with differential and platelets, LFT's; MUGA.
B) Physical exam- special attention to skin, hair, nails, eyes, heart, urine color.
C) Previous radiation to the chest or previous anthracycline history does worsen the chance of cardiotoxicity.
D) The precise role of mitoxantrone relative to idarubicin, doxorubicin or daunorubicin is still being developed.

ACTINOMYCIN D (also known as DACTINOMYCIN)
(COSMEGEN®)

I. MECHANISM OF ACTION
Dactinomycin intercalates with DNA to impair RNA chain elongation during protein synthesis.

II. PHARMACOKINETICS
A) Dactinomycin is given intravenously because oral absorption is very poor.
B) It is rapidly taken up by various tissues, but especially the bone marrow. This drug leaves the tissues very slowly.
C) The metabolism and elimination of actinomycin are poorly described and few metabolites are known. The parent drug has been found in urine and bile but a large fraction of a dose is not accounted for.

III. DOSAGE AND ADMINISTRATION
A) Dactinomycin is usually given IV bolus over a few minutes.
B) It is a vesicant; this drug should not be filtered.

IV. TOXICITY
A) Bone Marrow - Neutropenia and thrombocytopenia occur within 8 to 14 days and the counts recover by day 25. This is the dose-limiting side effect.
B) Emesis - Actinomycin D is highly emetogenic. Emesis occurs within the first few hours and can last for a day. Justifies 5-HT_3RA use.
C) Gastrointestinal - Mucositis and diarrhea occur frequently and, if severe enough, can be reasons to withhold further therapy. Less commonly, patients may complain of anorexia, abdominal pain, or proctitis.
D) Dermatological - Actinomycin D is a vesicant. It can cause radiation recall at sites of previous irradiation. Alopecia often occurs within 7 to 10 days but is reversible with discontinuation of therapy.

V. CLINICAL MONITORING
A) Labs-CBC with differential and platelets, liver function tests.
B) Physical exam-mouth, skin, IV access.
C) Check the history for radiation therapy.
D) Strong antiemetics should be ordered with actinomycin D.

BLEOMYCIN
(BLENOXANE®)

I. MECHANISM OF ACTION

A cell cycle specific agent that produces free radicals which attack lipid membranes and bleomycin directly causes double and single strand breaks in DNA. Resistance mechanisms include increased drug deactivation, decreased accumulation, and rapid repair of DNA.

II. PHARMACOKINETICS

A) Bleomycin is degraded by an enzyme called aminohydrolase, which is found in many tissues but in minimal amounts in the lungs and skin.
B) 45-70% of a dose is eliminated in the urine. Administration of bleomycin to patients with a creatinine clearance under 60 mL/min may increase the risk of pulmonary toxicity.
C)

III. DOSAGE AND ADMINISTRATION

Bleomycin can be given SC, IM or IV. Dosing is usually expressed in units with 1 unit equaling 1.2 to 1.7 mg. A test dose of 1 unit is usually given IM to test for hypersensitivity. It has also been given as an intrapleural sclerosing agent for pleural effusions at a dose of 60 units.
Note: Despite the test dosing of bleomycin recommended by the manufacturer especially in lymphoma patients, acute hypersensitivity reactions or severe hyperpyrexia that led to acute fulminant death have been reported in patients who have been previously exposed to the test dose and the full doses of the drug without eliciting any reactions. In other words, the routine practice of employing a test dose in every patient in an attempt to identify or avoid the occurrence of these acute reactions may not be necessary (ML).

IV. TOXICITY

A) Bone marrow suppression is minimal.
B) Hypersensitivity- periorbital edema, urticaria, bronchospasm.
C) Fever- 25% of patients for up to 48 hours.
D) Cutaneous Reactions - 50% of patients. Erythema, induration, hyperkeratosis, and peeling on the fingers, hands, joints, feet, and areas of previous radiation. Patients may also develop hyperpigmentation, alopecia, and nail changes. Due to the lack of bleomycin-inactivating enzyme (bleomycin hydrolase) in the lungs and skin bleomycin toxicity occurs primarily in these organs.
E) Pulmonary- Several syndromes are recognized: bronchiolitis olbliterans organizing pneumonia (BOOP), eosinophilic hypersensitivity, and interstitial pneumonitis (most common). Subacute or chronic interstitial pneumonitis progressing to interstitial fibrosis, hypoxia, and death. IP occurs in 0 – 46% patients treated with bleomycin [Reference: Sleijfer S. *Chest* 2001;120:617 – 24].
    1. Symptoms- nonproductive cough, exertional dyspnea, fever, pleuritic pain; may result in progressive pneumonitis, dyspnea at rest, tachycardia and cyanosis. Starts gradually during therapy, but has been reported to occur up to 6 months after discontinuing bleomycin therapy.
    2. Decreased oxygen saturation and carbon monoxide diffusion capacity.
    3. PFT's only help if a dramatic drop occurs. Most patients have a decrease anyway with bleomycin
    4. Initially the physical exam and CXR may be unrevealing but later will be helpful [bilateral bibasilar infiltrates sometimes followed by diffuse interstitial and alveolar infiltrates]. CT examination typically reveals small linear and subpleural nodular lesions in lung bases.

5. Definitive diagnosis requires an open lung biopsy.
6. Risk factors include lifetime cumulative dose greater than 400 units, age over 70, underlying emphysema, radiation to the chest, concurrent oxygen therapy, and tobacco use.
7. Corticosteroids (60 – 100 mg/day) may help but their role is controversial.

Prevention: lower total cumulative dose. Several other agents have been studied in murine models as protective agents, namely cyclosporine A, amifostine and dexrazoxane with variable success.

V. CLINICAL MONITORING

A) Physical Exam- skin, lungs, heart, renal function.
B) History- radiation, pulmonary & cardiac, drugs such as cyclophosphamide or busulfan.
C) Labs- creatinine and BUN.
D) A test dose helps identify those patients at risk of anaphylaxis.
E) Oxygen therapy should be kept to a minimum, if ever used at all, in patients who have received bleomycin. Oxygen helps to form the free radicals, which result in pulmonary damage from bleomycin.
F) Absolute smoking cessation.
G) It is usually ordered in units not mg.

MITOMYCIN C
(MUTAMYCIN®)

I. MECHANISM OF ACTION

Although an antibiotic similar to doxorubicin, mitomycin acts as an alkylating agent. It is activated in vivo to an active alkylator of DNA. Activity appears to be greatest in hypoxic tumors. It is a non-cell cycle specific drug. Mitomycin is both a carcinogen and teratogen. Resistance is mediated by P-glycoprotein and cytosolic glutathione transferase.

II. PHARMACOKINETICS

A) Mitomycin is given parenterally.
B) Distributes significantly to the kidneys, cervix, skeletal muscle, lungs, intestines, stomach, and eyes. Mitomycin will enter ascites to achieve a concentration 40% of the plasma.
C) Mitomycin is metabolized in the liver but not by the cytochrome P-450 system. Only 10% of a dose is eliminated in the urine, leaving the rest to be removed extensively by the biliary tree. Based on limited data, it does not appear necessary to adjust the dose in liver dysfunction.

III. DOSAGE AND ADMINISTRATION

A) Because mitomycin is a vesicant, it is usually given IV push.
B) A short infusion through a central line when mitomycin is mixed in 100-150 mL may be done.
C) Continuous infusions have been used.
D) Bladder instillation may be done. Mix 20 mg in 20 mL sterile water. It is not absorbed systemically.

IV. TOXICITY

A) Pancytopenia - The effect on all three lines can be severe. Importantly, recovery might be delayed, necessitating a dosing interval of 6 - 8 weeks. Platelets and neutrophils are especially affected. It is dose related and cumulative from cycle to cycle.
B) Nausea and vomiting- modest in severity and may last several hours.
C) Dermatologic toxicity includes alopecia, nail bed banding, and vesicant activity if extravasation occurs. Ulcerations may not appear for 3 - 4 months or may appear soon after the event. Topical DMSO is the best-known treatment.
D) Veno-occlusive disease.
E) Hemolytic Uremic Syndrome-Microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure (HUS-TTP) can occur suddenly and without warning. It is similar to the pattern seen in thrombotic thrombocytopenic purpura (i.e., schistiocytes on smear; thrombocytopenia; and ARF). Occurs in patients who have received over 60 mg and is delayed for up to 4 months from the last dose. Mortality rate is 50%. Treatment is plasma exchange. Incidence increases with increase lifetime doses: 1.6% develops it at 50 mg/m^2, increasing to 10.8% at a dose of 50 – 69 mg/m^2 and 27.8% patients at a dose of 70 mg/m^2.
F) Pulmonary- Syndrome of dyspnea, cough, fatigue and eventual respiratory decompensation. May respond to corticosteroid treatment.

V. CLINICAL MONITORING

A) Labs-CBC, SCr, LFT's.
B) Be aware that the recovery of the bone marrow may take 6-8 weeks from the administration of mitomycin.
C) HUS from mitomycin may be fatal within weeks if not rapidly addressed.