

ALKYLATING AGENTS

CYCLOPHOSPHAMIDE AND IFOSFAMIDE/MESNA (CYTOXAN[®] / IFEX[®] / MESNEX[®])

I. MECHANISM OF ACTION

Both drugs belong to the class of antineoplastics known as the alkylating agents. They need to be activated in the liver prior to exerting their cytotoxic activity. Once activated, they react with DNA to form strong chemical bonds, which render the DNA inactive and stop DNA synthesis. The 4-OH metabolite is the chief antitumor and immunosuppressant agent. The 4-OH metabolite crosses cell membranes readily and is then transformed into phosphoramidate mustard, which is the alkylating moiety.

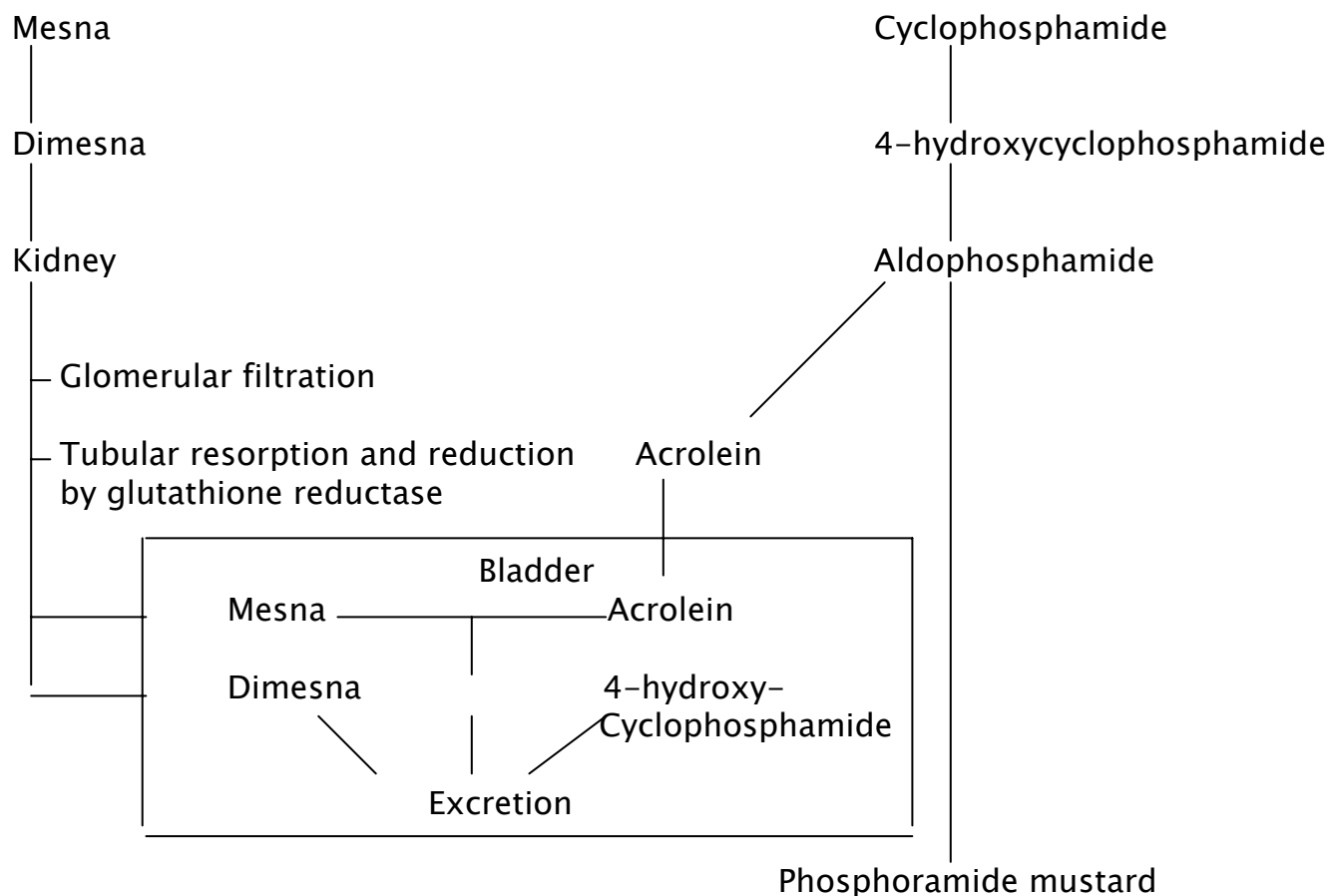
Resistance occurs through several mechanisms. Decreased transport across the cell membrane, decreases in intracellular sulfhydryl content, elevated glutathione concentrations increased repair of alkylator damage.

II. PHARMACOKINETICS

- A) Absorption – 74% (34 – 97%) of a dose of cyclophosphamide reaches the blood stream. Ifosfamide is not given orally because first pass metabolism leads to a metabolite which causes excessive CNS toxicity.
- B) Metabolism – Both drugs are metabolized by the liver to active and inactive metabolites. Cyclophosphamide induces its own metabolism with repeated doses. The liver has a large capacity to metabolize these drugs such that dosage adjustment in liver disease is apparently not required. Children metabolize these drugs faster than adults. Chloroacetaldehyde is a metabolite of ifosfamide and is a relative of chloral hydrate and explains the CNS effects of ifosfamide.
- C) Elimination– Active metabolites (80% of a dose) are eliminated through the kidneys but dosage adjustment in renal dysfunction is not necessary.

III. DOSAGE AND ADMINISTRATION

- A) Cyclophosphamide is available as an oral tablet and an IV formulation. The oral formulation should be taken during the day and prior to the evening meal at the latest. This will allow excretion of the active metabolite of cyclophosphamide prior to going to bed. Otherwise, the active drug will remain in the bladder and cause hemorrhagic cystitis.
- B) Cyclophosphamide IV can be given IV bolus or infused as a minibag.
- C) Ifosfamide is also given as a short infusion. MESNA is given at the start and then after ifosfamide therapy. The usual dosing scheme is that the total dose of MESNA is 60% of the ifosfamide dose. It is given in 3 bolus doses of 20% of the ifosfamide dose at time 0 with the ifosfamide and then 4 and 8 hours later. Alternatively, MESNA is given at 100% of the dose of ifosfamide and given as a continuous infusion during the ifosfamide and for 24 hours after. MESNA has also been given orally by doubling the IV bolus dose and giving it in the same schedule before and at 4 and 8 hours after each ifosfamide dose. Oral mesna tablets are now commercially available. The recommended dose of oral mesna is 40% of the cyclophosphamide or ifosfamide dose, given prior to antineoplastic agents and then repeated at 2 hours and 6 hours after the cyclophosphamide/ifosfamide dose.



IV. TOXICITY

- A) Myelosuppression – Mostly toxic to WBC, sparing the platelets. Nadir in 10 days, recovery in 20. Cyclophosphamide has been observed to be stem cell sparing, meaning that counts recover even with extremely high doses, which is not the case for all alkylating agents (e.g., busulfan).
- B) Emesis – Dose related and patient specific. Centrally mediated. Dose related. Delayed nausea and vomiting is common. Onset may not occur for 8 hours. The incidence of nausea/vomiting is high, occurring in about 58% of patients treated. Standard antiemetic therapy is used to control these reactions. It is more common with bolus administration. Nausea/vomiting can last for 3 days on average and longer periods of delayed emesis have been observed.
- C) Sterility – azospermia, amenorrhea, ovarian atrophy. May be reversible.
- D) Teratogenicity – Toxic if given in the first trimester.
- E) Carcinogenesis – Second malignancies, usually an acute leukemia, may occur years after treatment with cyclophosphamide.
- F) Pneumonitis – Nonproductive cough, dyspnea, tachypnea, and cyanosis. CXR reveals diffuse interstitial changes, which occurs rarely.
- G) SIADH – decreased urine output within 6–8 hours of treatment, weight gain, increased urinary osmolarity, decreased serum osmolarity. This is seen with cyclophosphamide in doses of ≥ 50 mg/kg.

- H) Alopecia – 80–100% patients. Begins about 3 weeks after therapy. This is more common with bolus than with continuous infusion.
- I) Cardiotoxicity – Myocardial necrosis occurs at doses of 60mg/kg or greater, which are used in bone marrow transplantation. A sudden and severe onset of CHF with death in 10–14 days can occur. There may be ST segment depression, progressive heart failure, and pericarditis with or without tamponade. The contribution of prior doxorubicin and or radiotherapy to myocardial necrosis is unclear.
- J) Immunosuppression – Suppressed B and T cell function places the patient at risk for fungal, viral, or protozoal infections. Patients will also be nonreactive to a PPD. This effect lasts for about 4 weeks in most situations. In bone marrow transplant, this effect is taken advantage of to suppress host rejection of the transplanted foreign marrow.
- K) Hemorrhagic cystitis – Acrolein, an active metabolite passing through the urinary bladder, is toxic to the mucosa. We commonly worry about this effect in patients receiving ifosfamide or high dose cyclophosphamide, but it occurs occasionally in patients taking oral low doses of cyclophosphamide and who fail to drink an adequate amount and don't void frequently. The symptoms begin 1 to 2 days after administration and, on average, last for 9 days.

Therapeutic measures include forced diuresis, frequent voiding, continuous bladder irrigation, N-acetylcysteine bladder irrigation, alum irrigation, formaldehyde irrigation, and estrogen therapy. The newest and most sensible approach is **prevention** with IV mesna. Mesna (2-mercaptoethane sulfonate sodium) is not an antineoplastic, but serves as an inactive chemical to which the active cyclophosphamide or ifosfamide metabolite acrolein can bind instead of attacking the bladder mucosa. Mesna is in an inactive form in the blood stream but becomes active in the urine. Mesna can be given orally. Mesna should always be given with ifosfamide and high dose cyclophosphamide if hyperhydration is not being used.

- L) Nephrotoxicity – a Fanconi-like syndrome has been seen with ifosfamide, with damage to the renal tubules and a rise in creatinine.
- M) Neurologic – The most common CNS adverse reactions are confusion, drowsiness, hallucinations, and depressive psychosis, and occur in about 12% of all patients treated with ifosfamide. Other less common effects include ataxia, dizziness, disorientation and cranial nerve dysfunction, with occasional seizures and coma reported. Patients with impaired renal function may have a higher incidence of adverse CNS reactions.

V. CLINICAL MONITORING

- A) Labs– U/A, CBC with differential and platelet, chemistry panel for sodium.
- B) Baseline CXR.
- C) Physical exam– hair, heart, lungs, renal function.
- D) Antiemetics should be given for 1–5 days since nausea and vomiting can be delayed (with the higher doses).

BUSULFAN
(MYLERAN[®]; BUSULFEX[®] = IV FORMULATION)

I. MECHANISM OF ACTION

- A) A non cell cycle specific alkylating agent that forms irreversible covalent bonds with DNA. It forms DNA–DNA interstrand crosslinks and DNA–protein cross links.
- B) At lower doses it tends to spare platelets and lymphocytes, but at higher doses (those used in BMT), it is toxic to platelets and lymphocytes.
- C) Resistance is due to impaired cell entry, or increased glutathione transferase activity.

II. PHARMACOKINETICS

- A) Absorption is nearly complete.
- B) Distribution is wide; CSF: plasma concentration ratio of 1.3 to 1 (range 0.9 – 1.7).
- C) Plasma protein binding is only 7.4%.
- D) Clearance is totally hepatic. There is a linear relationship between dose and AUC. Clearance is more rapid in children than adults.

III. DOSAGE AND ADMINISTRATION

- A) Usually given as an oral product. Recently marketed as an injectable (note the oral dose and the IV dose are NOT the same).
- B) In the treatment of chronic phase CML, it is given in a dose of 4–12 mg/day (or 0.1 mg/kg/day) until the WBC reaches $20 \times 10^9/L$. It is difficult to titrate the dose and WBC without overshooting the targeted WBC count.
- C) Food delays absorption.
- D) In BMT the oral dose is commonly 0.75 mg/kg q6h for 16 doses (other programs around the country use 1 mg/kg x 16 doses, but have the availability to perform busulfan assays and hence modify dosages to prevent toxicity). The IV dose in adults is 0.8 mg/kg IBW or ABW, whichever is lower. Infuse over 2 hour. Dosing in children is different.
- E) Because of the epileptogenic effects of high dose busulfan, all patients should receive anticonvulsant therapy (e.g., phenytoin or lorazepam).
- F) Children exhibit a more rapid clearance and will need a higher dose.
- G) Blood concentration monitoring is available at FHCRC Seattle and in Philadelphia.

IV. TOXICITY

- A) Neutropenia is the chief adverse effect of busulfan.
- B) Interstitial pneumonitis. Is most common with long–term low dose therapy. Can occur in the first year but the average age of onset is 4 years. It is usually fatal within 4–6 months. The IP presents with fever, nonproductive cough, dyspnea, and hyperplasia of type II pneumocytes.
- C) Gynecomastia.
- D) Addisonian symptoms – busulfan lowers ACTH stores in the pituitary.
- E) Amenorrhea/testicular cancer.
- F) Teratogen.
- G) Emesis– high doses may occasionally be emetogenic but not always.
- H) VOD.
- I) Cataracts.
- J) Skin discoloration – brown pigmentation.

CARMUSTINE (BCNU) (BiCNU[®]; GLIADEL[®])

I. MECHANISM OF ACTION

- A) At physiologic pH, BCNU decomposes to isocyanate and chloroethyldiazonium hydroxide. The latter compound forms DNA–DNA crosslinks and DNA–protein cross–links.
- B) BCNU is non cell–cycle specific.
- C) Resistance is due to increased concentration of guanine–O⁶–alkyl–transferase.

II. PHARMACOKINETICS

- A) Immediately after injection, BCNU crosses many lipid barriers. The CSF concentration is 50% of plasma. There is also rapid decomposition in aqueous solution.
- B) BCNU also undergoes rapid hepatic biotransformation to form inactive metabolites.

III. DOSAGE AND ADMINISTRATION

- A) In order to improve solubility, BCNU requires some ethanol for solubilization and then dilution in 100 – 250 mL D₅W. Administer over 2 hours.
- B) Carmustine is available as an injectable (100 mg/vial)
- C) Carmustine is also available as an implantable wafer 7.7 mg (by neurosurgeon). Up to eight wafers are to be placed into the resection cavity (if the size and shape allows it).

IV. TOXICITY

- A) Delayed neutropenia so that the nadir occurs in 3–5 weeks with resolution in 6 weeks. On rare occasions, carmustine may cause a non–pruritic syndrome, edema, bullae formation, and desquamation.
- B) BCNU is a venous irritant and may cause pain and burning near the injection site.
- C) Emesis is strong enough to require a serotonin antagonist.
- D) Elevated LFT
- E) Pulmonary fibrosis: may be sudden onset or insidious. Thought to be related to cumulative lifetime dosing. Doses greater than 450 mg/m² associated with a greater incidence. A CXR shows interstitial pneumonia. On PFTs the patient may have diffusion and restrictive defects.
- F) Optic neuroretinitis
- G) Recall dermatitis.

CHLORAMBUCIL (LEUKERAN®)

I. MECHANISM OF ACTION

Non cell-cycle specific alkylating agent that forms irreversible covalent bonds with DNA.

II. PHARMACOKINETICS

- A) Bioavailability is 75% when taken with food and less so in the fasting state.
- B) 99% plasma protein bound.
- C) Deposits in adipose tissue have led to delayed myelosuppression.
- D) At least 50% of a dose is hydrolyzed and eliminated as inactive metabolites in the urine.

III. DOSAGE AND ADMINISTRATION

Usually given as oral pulsed therapy with prednisone to treat CLL. Available as 2 mg tablets. No dosage adjustment in renal impairment is required.

IV. TOXICITY

- A) The dose limiting adverse effect is myelosuppression.
- B) Seizures have been seen at high doses (e.g., 144 mg/m²).
- C) Drug fever.
- D) Rash.
- E) Carcinogenesis/mutagenesis/teratogenesis.
- F) Pulmonary fibrosis.
- G) Sterility.

DACARBAZINE (DTIC) (DTIC-DOME®)

I. MECHANISM OF ACTION

- A) Metabolized by the cytochrome P-450 system to a carboxamide, a methyldiazonium ion, and formaldehyde.
- B) The methyldiazonium compound alkylates DNA.
- C) Noncell cycle specific.

II. PHARMACOKINETICS

- A) No schedule dependence to PK.
- B) Plasma protein binding is 20%. Little drug in the CSF.
- C) About 50% of a dose is eliminated in the urine as parent drug.

III. DOSAGE AND ADMINISTRATION

- A) Light sensitive.
- B) Stable for 8 hours after compounding at room temperature.
- C) Sometimes given as single large bolus or else daily for 5 days. The schedule does not affect efficacy or toxicity.
- D) Dose escalation leads to hypotension and flu-like symptoms.
- E) Venous irritant but not vesicant.

IV. TOXICITY

- A) Neutropenia/thrombocytopenia.
- B) Severe emesis requiring a 5HT₃ antagonist.
- C) Chemical hepatitis.
- D) Flu-like symptoms, starting day 7 and lasting up to day 21 in some instances
- E) Hypotension secondary to high doses of citric acid in high doses of DTIC leading to chelation of calcium and profound hypocalcemia.
- F) Photosensitivity.
- G) Alopecia.
- H) Facial flushing.
- I) Venous irritant.

LOMUSTINE (CCNU) (CeeNU[®])

I. MECHANISM OF ACTION

An atypical alkylating agent that forms covalent bonds with DNA and intracellular protein.

II. PHARMACOKINETICS

- A) Similar to carmustine. There is also hepatic conversion to the 4-OH metabolite via the cytochrome P-450 history.
- B) Plasma protein binding is only 15–30%

III. DOSAGE AND ADMINISTRATION

- A) Taken orally on an empty stomach.
- B) Available as capsules of 100 mg, 40 mg, and 10 mg with two of each in a box.
- C) Usually dosed at 6-week intervals.

IV. TOXICITY

- A) Delayed neutropenia so that the nadir occurs in 3–5 weeks with resolution in 6 weeks.
- B) Emesis.
- C) When given with cranial irradiation, cortical blindness has occurred.
- D) Interstitial nephritis.
- E) Mutagen/carcinogen/teratogen.
- F) Secondary myelodysplastic syndrome.
- G) Rarely, there may be stomatitis, alopecia, elevated LFTs.

MECHLORETHAMINE (NITROGEN MUSTARD) (MUSTARGEN®)

I. MECHANISM OF ACTION

Mechlorethamine is a bifunctional alkylating agent and exerts its chemotherapeutic effects by substituting alkyl groups for hydrogen ions in a number of organic compounds. Mechlorethamine reacts readily with phosphate, amino, hydroxyl, sulfhydryl, carboxyl, and imidazole groups on amino acids. DNA-DNA interstrand and DNA-protein crosslinking occur, leading to DNA strand breakage and interference in DNA replication, transcription of RNA, and nucleic acid function. Cellular functions such as protein synthesis and glycolysis are impaired. Besides being an antineoplastic, mechlorethamine also is a mutagen and radiomimetic.

II. PHARMACOKINETICS

- A) Absorption – Usually given IV. Used topically for mycosis fungoides.
- B) Distribution – Following IV administration, mechlorethamine is rapidly transformed to its active form; unchanged drug is undetectable in the blood a few minutes after administration. Intracavitary injection results in incomplete absorption of mechlorethamine, probably due to rapid inactivation of the drug by the body fluids.
- C) Metabolism – The active form of mechlorethamine reacts with various components of the cell before becoming inactivated by the body fluids.
- D) Elimination – Metabolites of the drug are excreted in the urine.

III. DOSAGE AND ADMINISTRATION:

Available as a 10 mg injection. Administered primarily intravenously for the treatment of Hodgkin's disease and NHL. Also administered as a intracavitary injection (as pleurodesis) for pleural and pericardial effusions. This is very painful and no better than other agents.

IV. TOXICITY

- A) Myelosuppression – The granulocytes and platelets reach a nadir in 8–14 days. Persistent pancytopenia and agranulocytosis also have been reported.
- B) Emesis – Nausea/vomiting are the major dose-limiting adverse GI symptoms associated with mechlorethamine therapy and are presumably due to CNS stimulation. This reaction occurs in 90% of patients. These effects generally occur within 1 hour and usually last 8–24 hours. Vomiting can be extreme and could precipitate vascular accidents in patients prone to hemorrhagic accidents. Antiemetics may prevent or alleviate these symptoms.
- C) Vesicant – Patients receiving mechlorethamine should be observed for an injection site reaction. Mechlorethamine is a strong vesicant, and inhalation of the dust as well as contact with the eyes and skin should be avoided. If eye contact occurs, flush eyes with copious amounts of sodium chloride or some other balanced salt solution, then have an ophthalmologic examination. If skin contact occurs, flush affected area with water for at least 15 minutes, then apply 4% (or one-sixth molar) thiosulfate solution. Extravasation of mechlorethamine can lead to pain, swelling, erythema, induration, sloughing, or thrombophlebitis. As much of the infiltrated drug as possible should be aspirated, and the local inflamed area should then be infiltrated with an isotonic sodium thiosulfate injection. Cold compresses should be applied for 6 to 12 hours. The thiosulfate solution is made by mixing 4 ml of a 10% solution with 6 ml of sterile water.

- D) Hypersensitivity – Hypersensitivity can develop, especially with topical application, and can prevent further therapy. The reaction appears to be a delayed hypersensitivity.
- E) Fertility/Teratogenicity – Mechlorethamine is a pregnancy category D drug and can cause fetal abnormalities; however, reports have been published of women delivering normal infants after taking mechlorethamine during pregnancy. Gonadal suppression in males and females is common, and patients should be aware of this possibility. Atrophy of the testis or ovary has been reported. Amenorrhea also is seen in women. Fertility and normal menses can return but also could be lost with mechlorethamine therapy.
- F) Dysgeusia – metallic taste.

MELPHALAN **(ALKERAN®)**

I. MECHANISM OF ACTION

A non cell cycle specific alkylating agent that forms irreversible covalent bonds with DNA.

II. PHARMACOKINETICS

- A) Oral absorption is poor with 25–50% of a dose being recovered intact in the stool.
- B) Food decreases bioavailability even further.
- C) Most of an absorbed dose is nonenzymatically hydrolyzed to inactive hydroxy derivatives within minutes of administration.
- D) 21–34% of a dose is recovered as unchanged drug in the urine.
- E) Renal dysfunction seems to enhance bone marrow suppression from melphalan and a dosage adjustment has been recommended for patients with a BUN > 30 mg/dL.

III. DOSAGE AND ADMINISTRATION

- A) Available as oral tablet (2 mg) or IV form (50 mg vials).
- B) The tablet is best absorbed on an empty stomach.
- C) The injectable requires ethanol to stabilize the solution. The final diluted product is compounded in normal saline and is stable for 1 hour. The IV route is primarily reserved for BMT preparative regimens. Doses used range from 140 – 220 mg/m².

IV. TOXICITY

- A) Neutropenia and thrombocytopenia are the dose limiting adverse effects. Occasionally recovery of the marrow is delayed.
- B) Dermatitis.
- C) Alopecia.
- D) Pulmonary fibrosis.
- E) Secondary myelodysplastic syndrome or AML.
- F) Delayed nausea and vomiting is common with doses used in HSCT. Use delayed nausea and vomiting prophylaxis (metoclopramide and dexamethasone or aprepitant and dexamethasone) for HSCT doses.

PROCARBAZINE (MATULANE®)

I. MECHANISM OF ACTION

- A) Procarbazine must be activated by the cytochrome P-450 system to exert its cytotoxic effects. Several active metabolites can form.
- B) The exact mechanism(s) of action of procarbazine is not clear, but the drug appears to have several sites of action in the cell.
 - 1. Procarbazine may inhibit the incorporation of thymidine, deoxycytidine, formate, adenine, and 4-amino-5-imidazolecarboxamide into DNA.
 - 2. Prevent the utilization of orotic acid in RNA synthesis.
 - 3. Prevent the utilization of leucine in the synthesis of proteins.
 - 4. Procarbazine may also directly damage DNA by direct alkylation.
- C) The drug is thought to inhibit mitosis by extending the interphase stage of cell division and causing breakage of chromatids. The cytotoxic effects of procarbazine are only evident in cells, which are rapidly proliferating and actively synthesizing DNA. It appears to be most active during S and G₀.

II. PHARMACOKINETICS

- A) Absorption – Procarbazine is rapidly and completely absorbed across the GI tract following oral administration.
- B) Distribution – The drug distributes widely throughout the body tissues, concentrating in the liver, intestinal wall, skin, and kidneys. Procarbazine readily crosses the blood-brain barrier.
- C) Metabolism – Undergoes extensive metabolism by cytochrome P450 enzymes or mitochondrial monoamine oxidase enzymatic conversion to form azoprocarbazine, which is then further metabolized into cytotoxic metabolites.
- D) Elimination – Both unchanged drug and its metabolites are excreted in the urine. Seventy percent of a dose can be found in the urine in the first 24 hours after a dose. Although specific guidelines for dosage adjustments in renal impairment are not available; reduced doses are recommended to avoid excessive toxicity in patients with a BUN greater than 40 mg/dL and/or serum creatinine greater than 2 mg/dL.

III. DOSAGE AND ADMINISTRATION: available as an oral 50 mg capsule.

IV. TOXICITY

- A) Myelosuppression – Bone marrow depression, resulting in neutropenia, thrombocytopenia, and anemia may occur, and patients with preexisting hepatic, renal or bone marrow depression are predisposed to developing severe procarbazine toxicity. Thrombocytopenia is more common than neutropenia or anemia. Hemolytic anemia can also occur. The nadir for platelets is around week 4. Anemia and neutropenia recover around week 4 to 6.
- B) Gonadal Suppression – Occurs in males and females commonly, and patients should be aware of this possibility. Atrophy of the testis or ovary has been reported. Amenorrhea also is seen in women. Fertility and normal menses can return but also could be lost with mechlorethamine therapy.
- C) Teratogenicity – Procarbazine is a known teratogen and should not be used during pregnancy. Both male and female patients should use barrier contraception when either is taking procarbazine because of its effects on germ cell lines.

- D) Disulfiram Reaction – A disulfiram–like reaction may occur in patients who drink ethanol while they are receiving procarbazine therapy; alcohol is thus contraindicated during procarbazine therapy. There are only case reports to support this recommendation and the true clinical significance has never been established.
- E) Monoamine Oxidase inhibition – Procarbazine is a monoamine oxidase inhibitor. Therefore, sympathomimetics, local anesthetics, tricyclic antidepressants, and foods with high tyramine content such as bananas, cheese, tea, coffee, wine, and cola should be avoided while receiving procarbazine therapy. This is a theoretical concern and has not been established by clinical experience as being clearly significant.
- F) GI Toxicity – Adverse oral and GI symptoms associated with procarbazine toxicity include nausea/vomiting, diarrhea, anorexia, and stomatitis. The nausea/vomiting can occur independently of any ethanol ingestion. The emesis can be severe but prevented with dose titration. Severe diarrhea or ulcerative stomatitis may cause hemorrhagic enteritis or intestinal perforation, possibly leading to death and procarbazine therapy should be discontinued if these effects occur.
- G) Neurologic – Many adverse CNS effects have occurred in patients during procarbazine therapy including paresthesias, neuropathies, depression, manic reactions, acute exogenous psychosis, hallucinations, headaches, dizziness, nervousness, apprehension, nightmares, insomnia, ataxia, tremors, coma, confusion, delirium, and seizures. Procarbazine therapy should be discontinued if neuropathies, paresthesia, or confusion occurs. CNS effects can occur in up to 30% of patients. Patients should be counseled in advance regarding these effects.
- H) Pulmonary – Pulmonary problems often occur during procarbazine therapy and include pneumonitis, pleural effusion, and cough.
- I) Constitutional Symptoms – Constitutional symptoms such as fever, chills, diaphoresis, myalgia, and arthralgia may occur. Skin rashes also can occur.

STREPTOZOCIN (ZANOSAR[®])

I. MECHANISM OF ACTION

- A) Undergoes spontaneous degradation to form a reactive molecule that forms a covalent bond with DNA.
- B) Inactivates O⁶-alkylguanine transferase, an enzyme some cancer cells use to reverse binding by some alkylating agents.
- C) Interferes with glyconeogenesis.
- D) Causes permanent damage to the pancreatic beta cell leading to a diabetic state.
- E) Non cell-cycle specific.

II. PHARMACOKINETICS

- A) Given intravenously.
- B) Decomposes and disappears from the plasma within 3 hours.
- C) Concentrates in liver, kidney, intestines, and pancreas.
- D) Metabolites cross the blood-brain barrier and achieve concentrations equal to plasma.
- E) Only 15% of a dose is recovered in the urine. The rest is either metabolized by the liver or excreted in the breath.

III. DOSAGE AND ADMINISTRATION:

- A) Available as an IV formulation (1 g vial) and administered as a short IV infusion or a CIVI.
- B) In patients with renal impairment it is recommended that the dose of streptozosin is reduced or the drug is discontinued due to cumulative drug-induced nephrotoxicity.

IV. TOXICITY

- A) GI – Very emetogenic. Requires a serotonin antagonist. Emesis tends to worsen over the time of each course, usually 5 days each month.
- B) Hematological – Not very myelosuppressive.
- C) Nephrotoxicity–Most serious side effect and stopping therapy should be considered. Occurs in 45–65% of patients. Initially presents with hypophosphatemia. Proteinuria and azotemia reflect further damage. Fanconi's syndrome and frank anuria have been seen. Permanent tubular damage may occur. The effect may not be dose related. Renal neoplasms may occur with streptozocin (it is chemically similar to carcinogenic nitrosoamines).
- D) Venous irritant–Experienced with bolus administration. Administer over 30 minutes or longer. Preadministering a 50/50 solution by volume of 1% lidocaine and NS or D₅W may reduce the pain as well, but this solution should not be added to the streptozocin.
- E) Endocrine–Initially there is hypoglycemia as beta cells damaged by streptozocin dump their insulin. Eventually, after depleting their stores of insulin, hyperglycemia develops.
- F) Hepatic – jaundice.

V. CLINICAL MONITORING

- A) CBC with differential.
- B) Be sure an adequate antiemetic regimen has been ordered.
- C) Follow renal function closely (SCr and BUN) as well as electrolytes.
- D) Follow glucose levels and use insulin or dextrose as needed.
- E) Venous irritation is mostly a rate-related problem and slowing the infusion usually helps.

TEMOZOLOMIDE (TEMODAR®)

I. MECHANISM OF ACTION

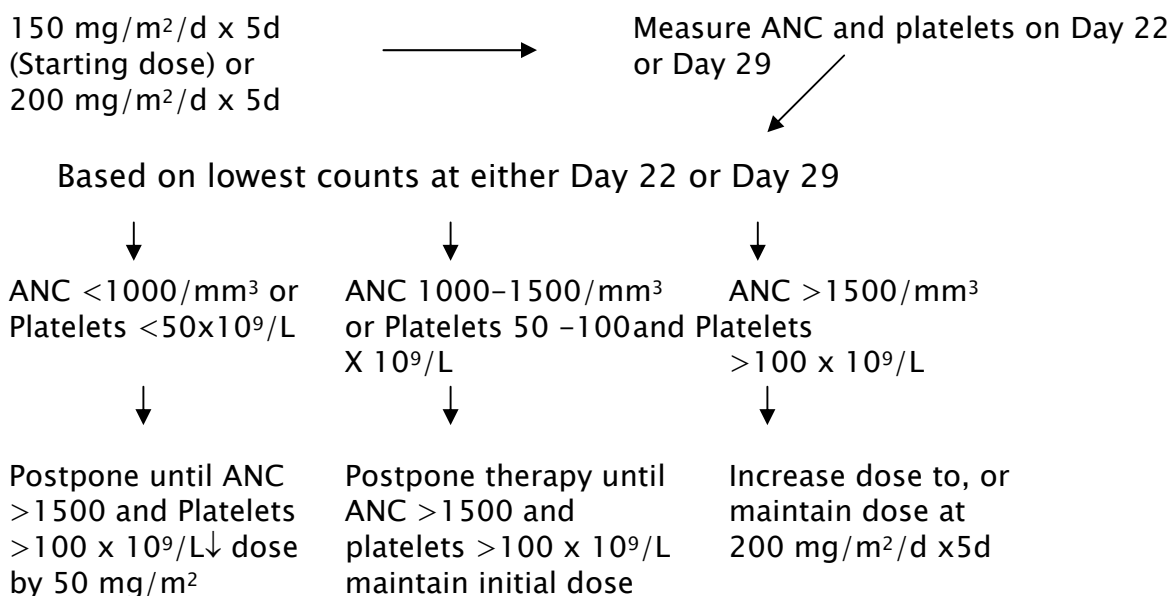
Undergoes conversion at physiologic pH to the reactive compound MTIC, which is 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide. The cytotoxicity of MTIC is primarily due to alkylation of DNA.

II. PHARMACOKINETICS

- A) Absorption is complete with peak plasma levels occurring within 1 hour
- B) Metabolism and Elimination: Hydrolyzed to MTIC and to temozolomide acid. Cytochrome P450 enzymes play a minor role in the metabolism.

III. DOSAGE AND ADMINISTRATION

- A) Initial dose of 150 mg/m² orally once daily for 5 consecutive days per 28 day cycle. The next cycle should not be started until the ANC is above 1.5 x 10⁹/L and the platelet count is above 100 x 10⁹/L. During treatment a Day 22 CBC should be obtained. Suggested dose modifications are listed on the next page.
- B) Temozolomide should be used with caution in patients with severe renal impairment, but exact dose adjustments are not available.



- C) Capsules available as 5 mg, 20 mg, 100 mg, or 250 mg.
- D) Capsules should not be opened or chewed. Swallow whole with a glass of water.

IV. TOXICITY

- A) Most frequent side effects are nausea, vomiting, headache, and fatigue.
- B) Thrombocytopenia and neutropenia are the dose limiting adverse events (see above for dose modification). The platelet nadir is typically 26 days after a course and the ANC nadir is day 28. Count recovery typically occurs within 14 days of the nadir. Grade 3/4 anemia, leukopenia, neutropenia and thrombocytopenia occur in 4%, 11%, 14%, and 19% of patients, respectively.

V. CLINICAL MONITORING – CBC with differential.

THIOTEPA **(THIOPLEX®)**

I. MECHANISM OF ACTION

A prodrug converted to an active form that covalently binds to DNA.

II. PHARMACOKINETICS

- A) After injection, the drug is rapidly converted by the cytochrome P450 system to TEPA, which has some activity, and is itself cleared.
- B) No drug is eliminated in the urine.
- C) Plasma protein binding is only 40%.
- D) Saturable clearance is noted at doses over 30 mg/m².

III. ADMINISTRATION

- A) Given IV bolus, IV continuous infusion, intrathecal, or intravesical.
- B) For intravesical use, mix 60 mg in 60 ml sterile water for injection, instill in the bladder and hold there for 2 hours while rolling the patient 90 degrees each 15 minutes.
- C) Data is limited regarding elimination in hepatically or renally impaired patients, but hepatic impairment may decrease clearance. The urinary clearance of thiotepa and TEPA is complete within 6–8 hours and 8–12 hours, respectively. Alkylating activity, however, remains and suggests unidentified metabolites.

IV. TOXICITY

- A) Bone marrow suppression is the dose limiting adverse effect. The neutrophil nadir is approximately day 7–10 and the platelet nadir may be in 21 days. Bone marrow effects are seen even with intravesical therapy.
- B) Occasionally causes emesis, dizziness, and headache.
- C) Secondary AML or solid tumors have been seen after thiotepa use.
- D) Mucositis–BMT doses.
- E) Dermatitis–Metabolites can accumulate in skin folds and dressings. Frequent showers may reduce discomfort. On rare occasions thiotepa may cause a non-pruritic syndrome, edema, bullae formation, and desquamation.