THE ANTIMETABOLITES

FOLATE ANTAGONISTS

METHOTREXATE (MTX)

I. MECHANISM OF ACTION

A) Methotrexate is a modified form of folic acid.
B) Folic acid is normally converted to its active form by the enzyme dihydrofolate reductase (DHFR). Folic acid/folates are necessary for the synthesis of purine nucleotides, which in turn are essential for DNA synthesis and cell division.
C) Methotrexate binds to DHFR and prevents folic acid’s contribution to DNA synthesis in both malignant and benign cells.
D) Transmembrane transport of methotrexate into the cell occurs initially by a carrier protein. There are a limited number of such transport proteins per cell. At high concentrations of methotrexate, all the carriers are occupied and methotrexate enters the cell by simple diffusion. Alterations in the carrier proteins can be a source of resistance. The newer antifolates such as trimetrexate are not dependent upon the carrier proteins for entry and may be active in tumors resistant to MTX.
E) Once inside the cell methotrexate forms larger chains of molecules called polyglutamates which are active binders to DHFR and are too big to leave the cell. Binding to DHFR is 100 times greater than the parent drug. L-asparaginase prevents the formation of these larger molecules and, therefore, halts the activity of methotrexate. Formation of these polyglutamates inside the cell happens more readily in cancer cells than in normal cells. The polyglutamates bind not only to DHFR but also to thymidylate synthetase. AICAR transformylase, and GAR transformylase. The latter two enzymes use one-carbon groups from MTX to synthesize purines.
F) Methotrexate is a phase specific drug, acting during S phase. The minimum serum concentration known to affect cancer cells or bone marrow cells is $1 \times 10^{-8}$ M or 0.01 microM. Gastrointestinal epithelium is inhibited at 0.005 microM.
G) Methotrexate is unique among antineoplastic drugs because it has an agent to rescue normal cells from its toxic effects. Calcium leucovorin (also known as citrovorum factor or folinic acid or 5-formyl–tetrahydrofolate) is an active form of folic acid just like the active form of folic acid created by DHFR. Calcium leucovorin is given after methotrexate and often exactly 24 hours after methotrexate in order to allow methotrexate to inhibit cancer growth. Calcium leucovorin is transported across cell membranes by the same carrier protein as methotrexate, but it does not passively diffuse across as methotrexate does. When high concentrations of leucovorin cross the membrane, MTX is forced to efflux from the cell. Once across the membrane, calcium leucovorin can serve as the necessary factor for cell DNA synthesis which methotrexate was blocking. When given with methotrexate, leucovorin can impair polyglutamation. In order for calcium leucovorin to be effective, it must be in sufficient concentration to out compete methotrexate for the carrier proteins. This is why we obtain methotrexate levels to determine if the dose and duration of calcium leucovorin therapy is adequate relative to the methotrexate serum concentration. Calcium leucovorin should be administered within 40 hours of MTX to be effective.
H) Resistance can be de novo or acquired. It can occur via the following mechanisms: decreased transport of MTX into the cell; decreased polyglutamation of MTX; increased levels of DHFR (usually based on amplification of the DHFR gene); and alterations in the affinity of DHFR for MTX.

I) In the allogeneic BMT setting, methotrexate is used with cyclosporine or tacrolimus to prevent graft–versus–host disease in a dose of 5–15 mg/m² given on several specified days. It is used for its immunosuppressant effects, not its antitumor effects. Plasma concentration monitoring or leucovorin rescue are not usually necessary. Occasionally, however, because mucositis may be worse when methotrexate is given for GVHD, leucovorin is given in four doses a day after each methotrexate dose if the patient has grade III or IV mucositis.

II. PHARMACOKINETICS

A) Absorption– usually administered IV except in some leukemia, lymphoma, or breast protocols in which case the entire oral dose is usually well absorbed. Oral doses over 50 mg/m² should be divided.

B) Distribution– Volume of distribution equals total body water. Methotrexate will penetrate into pleural effusions or ascites. Penetration into CSF is usually inadequate except at extremely high doses. Intrathecal methotrexate is given for CNS involvement. Approximately 50 – 60% is bound to plasma proteins.

C) Metabolism– 20–50% of a dose is metabolized in the liver and the gut wall.

D) Elimination– 50–80% is eliminated as unchanged drug in the urine. Actively secreted in the proximal tubule, so that probenecid, penicillins, aspirin, and NSAID all may decrease elimination. Cephalosporins, sulfamethoxazole, folic acid, and leucovorin may enhance renal elimination by competing for renal tubule reabsorption. A small fraction is eliminated in the bile and later reabsorbed in a process called enterohepatic recirculation. See guidelines and recommendations for dosing antineoplastic agents in renal failure (miscellaneous section).

III. DOSAGE AND ADMINISTRATION

A) High-dose defined as a dose over 1 gram/m².

B) Use high dose methotrexate cautiously in patients with a CrCL < 60 mL/min.

C) Hydrate with 50–150 mEq NaHCO₃ in 1000 mL D₅W at 125 mL/hour. Increase NaHCO₃ content and infusion rate as needed to obtain a urine pH > 7. Alkalinization may take several hours. Acetazolamide has been used to alkalinize the urine, but NaHCO₃ is the time-tested approach. Keep pH greater than 7 for 24 hours post dose.

D) Check urine pH with each void and do not begin MTX unless pH ≥ 7.

E) Keep urine output ≥ 100 mL/hour

F) Begin calcium leucovorin 24 hours from the START of the MTX infusion. Continue leucovorin until MTX concentration is ≤ 5 x 10⁻⁸ M. Initially give IV leucovorin if more than 45 mg is needed per dose or the patient is vomiting. Oral and IV doses of leucovorin are equally bioavailable at doses up to 45 mg but over 45 mg, IV should be used for reliable serum concentrations. NOTE: each protocol typically has its own recommendations for starting MTX. Please make sure that you read the specifics for each protocol.

G) Obtain MTX serum concentrations per protocol or else at 24, 48, and 72 hours from the START of the infusion. Acceptable serum concentrations are 5 microM at 24 hr and 1 microM at 48 hr. Concentrations above these readings at these times warrant increased calcium leucovorin doses. Different institutions use variations on these cutoff points at 24 hr and 48 hr.

H) At lower doses, MTX is not very emetogenic, but with the high dose regimens, aggressive antiemetic therapy should be employed.
I) Overdosage: There is an investigational product that is available via the NCI called carboxypeptidase G2, which is able to inactivate MTX. Carboxypeptidase G2 (CPG2) cleaves folates and folate analogues resulting in alternative routes of folate metabolism. CPG2 is of particular interest in anticancer therapy for several reasons. CPG2 rapidly converts methotrexate (MTX) into less toxic metabolites causing a rapid decline of MTX serum levels in animal models as well as in humans. Thus, CPG2 is a powerful rescue agent in patients receiving high-dose MTX and might circumvent life-threatening toxicity in patients with MTX intoxication. As CPG2 causes a predefined and considerable decline of MTX levels, this substance might be also attractive for MTX dose escalation studies. In addition, CPG2 has been used in antibody-directed enzyme pro-drug therapy.

J) Can be administered IV, IM, SQ, IT (intrathecal); intratubal for ectopic pregnancy

K) Intrathecal: Dose is typically 12 – 15mg. Most common with leptomeningeal disease; ALL regimens; Burkitt’s leukemia/lymphoma; carcinomatous meningitis; acute myeloid leukemia M4 and M5. Prophylaxis strategies are different to treatment strategies. No standard treatment strategy here at Shands. Suggested regimen in ECOG studies in patients with AML involve twice weekly IT MTX (sometimes alternating with IT cytarabine) until clearance of the CSF. Once clearance administer once weekly for a couple 2 – 4 weeks; then monthly for 4–6 doses. Request in a minimal volume and use preservative free solutions, or additionally can be requested in Elliott’s B solution (= “fake” CSF).

IV. TOXICITY

A) Myelosuppression– onset in 7 days, resolved by day 14. Can be ↓ with leucovorin.

B) Mucositis– 20% patients, onset in 3–7 days, resolution by day 14. Can ↓ with leucovorin.

C) Renal– precipitation of methotrexate crystals due to insolubility. Good hydration to maintain a urine output of at least 100 mL/hour and urine alkalinization to a pH of 7 or more will minimize crystallization. Solubility increases from 0.39 mg/mL at pH = 5 to 9.04 mg/mL at a pH = 7, a 23 fold increase. Renal toxicity manifests itself with poor urine output and a rising BUN and serum creatinine, but nephrotoxicity may occur with even a normal creatinine. Should maintain urinary pH for up to 24 hours post–MTX dosing.

D) Modify dosing for renal toxicity:
- CrCL 70 – 79 mL/minute: reduce MTX dose by 25%
- CrCL 60 – 69 mL/minute: reduce MTX dose by 37%
- CrCL 50 – 59 mL/minute: reduce MTX dose by 44%
- CrCL < 50 mL/minute: Consider alternatives


Hemodialysis: not dialyzable (0 – 5%); supplemental dose is not necessary
E) Liver – 60% of patients will have a rise in bilirubin. Patients taking methotrexate for only a short time period may have a transient rise in LFT’s but this is not clinically significant. Patients taking methotrexate on a long-term base may develop fibrosis and require a liver biopsy for diagnosis.

F) Pneumonitis- a rarely occurring result of methotrexate therapy characterized by fever, cough, and chest X-ray finding. Acute and reversible. Cough, dyspnea, eosinophilia, and pulmonary infiltrates.

G) Neurological- intrathecal methotrexate can cause headache, nuchal rigidity, and vomiting. Delayed toxicity appears as limb spasticity, dementia, or coma. Chemical arachnoiditis frequently occurs. Consider adding hydrocortisone to intrathecal injection. Triple intrathecal therapy is a common component of protocols and consists of MTX 12 mg plus hydrocortisone 15 mg plus cytarabine 50 mg.

H) Pleural effusions and ascites can act as reservoirs for methotrexate, as it slowly leaks back into the blood stream. Prolonged toxicity, especially myelosuppression, can occur and necessitates lengthening calcium leucovorin therapy.

I) Ileus or constipation also increases the risk of methotrexate toxicity due to gut reabsorption of methotrexate eliminated through the biliary tree.

V. CLINICAL MONITORING
A) Baseline CBC with differential and platelets, SCr, BUN, LFT’s and urine pH.
B) Baseline PE with attention to the oral cavity, pulmonary function, neurologic status, abdominal exam, and hydration status.
C) The physician’s orders should specify when calcium leucovorin should begin, at what dose, by what route, and for how long. In addition, timing of serum levels of methotrexate should be identified. Hydration and urine alkalinization should also be specified.
D) High dose methotrexate should not be administered until the urinary pH is 7 or greater. The urine pH should be maintained throughout the methotrexate infusion and for up to 24 hours after completion of the administration of high doses. Typical methods to alkalinize the urine include administering D5W with sodium bicarbonate.

VI. DRUG INTERACTIONS
A) Salicylates, sulfonamides, probenecid and high dose penicillin compete with methotrexate for transport and reduce renal tubular excretion. Salicylates and sulfonamides may displace methotrexate from plasma proteins, increasing methotrexate levels.
B) Cytarabine: increased formation of the cytarabine nucleotide can occur when methotrexate precedes cytarabine, thus promoting the action of cytarabine. Note in the HyperCVAD protocol, methotrexate level at conclusion of infusion must be checked and results verified prior to starting high dose cytarabine. If the methotrexate level is greater than 20 microM then reduce the dose of cytarabine.
C) NSAID’s
D) Vincristine: inhibits methotrexate efflux from cells leading to increased and prolonged methotrexate levels in the cells.
PEMETREXED
(ALIMTA®)

I. MECHANISM OF ACTION
A) A pyrrolo–pyrimidine analog of folic acid, chemically similar to lometrexol and methotrexate; it is somewhat similar structurally to raltitrexed.
B) Pemetrexed gains cell entry via the reduced folate carrier, and is a good substrate for the enzyme folylpolyglutamate synthase (FPGS), which leads to extensive intracellular polyglutamation; the predominant intracellular form is the pentaglutamate, which is substantially more potent than the pemetrexed itself or its monoglutamate. Polarity occurs via polyglutamation, resulting in enhanced cellular retention and a more sustained effect.
C) Pemetrexed and its polyglutamates inhibit at least four enzymes involved in folate metabolism and DNA synthesis: thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycaminamide ribonucleotide formyl transferase (GARFT), and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT). Cell death occurs via inhibition of any one of these enzymes, particularly during cell division. The multiple actions of pemtrexed are speculated to reduce development of drug resistance (eg, that acquired by overexpression of one of these enzymes).

II. PHARMACOKINETICS
A) Absorption– not available orally
B) Distribution– 80% protein bound; limited tissue distribution due to small volume of distribution (6 to 7 liters/m²).
C) Metabolism– Metabolic pathways have not been identified. The drug appears to undergo minimal metabolism (hepatic or other) based on urinary excretion data.
D) Excretion: elimination half-life of parent compound 2 to 4 hours; 70 to 90 % renally excreted as unchanged (dose modification is indicated in renal impairment; some phase II studies suggested if creatinine clearance less than 45 ml/min, dose should be withheld till it resolves).

III. DOSAGE AND ADMINISTRATION
As a single agent, the most frequently used dose in all tumor types has been 500 or 600 mg/m² given over 10 minutes once every 21 days.

IV. TOXICITY
In clinical trials, elevated pretreatment homocysteine (tHcy) level significantly predicted severe thrombocytopenia and neutropenia (with or without associated grade 3/4 diarrhea, mucositis, or infection). Elevated pretreatment level of methymalonic acid (MMA) has also been found to significantly and independently predict both grade 3 and 4 diarrhea and mucositis.
A) Myelosuppression– dose–limiting and strongly associated with elevated pretreatment levels of homocysteine; neutropenia (nadir usually on day 8)
B) Cardiovascular– grade 1 or 2 edema (21%) observed in NSCLC receiving every 3 week regimen in a phase II study.
C) CNS – fatigue (75%)
D) Gastrointestinal– nausea, vomiting, mucositis, diarrhea (associated with elevated pretreatment MMA levels)
E) Renal– reversible; usually mild renal dysfunction (up to 25%) of patients receiving the every 21–day regimen.
F) Liver—Reversible elevations of serum aminotransferases, alkaline phosphatase, and bilirubin (up to 80% of patients, all grades) during treatment with the every 3–week regimen of 500 or 600 mg/m²;

G) Dermatologic—A pruritic, painful, generalized skin rash (up to 85%) in every 21–day doses of 500 to 600 mg/m²; grade 3 rash (up to 40%); grade 4 rashes (<10%).

Note: Premedication with oral dexamethasone 4 mg twice daily for 3 days, beginning the day prior to the dose of pemetrexed, has been used to significantly reduce the incidence and severity of rash.
Folic acid (dose 350 micrograms to 5 mg daily) and vitamin B₁₂ (1000 to 1500 micrograms every 9 weeks) supplementation have been added and been shown to reduce incidences of toxicities and death associated with the drug.

V. CLINICAL MONITORING
A) Labs—CBC with diff, BUN/Cr, urine output, LFT’s with bilirubin
B) Pretreatment levels of tHcy and MMA levels are strongly recommended, especially in patients with poor nutritional status.
C) Physical exam—mouth, skin
PYRIMIDINE ANTAGONISTS

AZACITIDINE (5–AZA)
(VIDAZA*)

I. MECHANISM OF ACTION
   A) Azacitidine is a pyrimidine nucleoside analog of cytidine.
   B) It causes hypomethylation/demethylation of DNA. Demethylation may restore normal
      function to tumor-suppressor genes that are responsible for regulating cell differentiation
      and growth.
   C) It also has direct cytotoxicity on abnormal hematopoietic cells in the bone marrow,
      resulting in the death of rapidly-dividing cells, including cancer cells that are no longer
      responsive to normal growth control mechanisms.

II. PHARMACOKINETICS
   A) Absorption: Azacitidine is rapidly absorbed after subcutaneous administration, with peak
      plasma concentrations occurring in approximately 30 minutes. The bioavailability of
      subcutaneous azacitidine vs. IV azacitidine is 89%.
   B) Distribution: Mean Vd after IV dosing is 76 ± 26 L.
   C) Mean CL after SQ administration is 167 ± 49 L/hr, and mean half-life is 41 ± 8 minutes.
   D) Urinary excretion is primary route of elimination; fecal excretion accounts for <1% of an
      administered dose.
   E) Mean elimination half-life of azacitidine and its metabolites is about 4 hours and is similar
      after IV and subcutaneous administration.

III. DOSING AND ADMINISTRATION
   A) The recommended starting dose is 75 mg/m² SC daily for 7 days, repeat cycles Q 4 weeks.
      The dose may be increased to 100 mg/m² if no benefit is seen after two cycles. Patients
      should receive a minimum of 4 cycles (although attainment of complete or partial
      response may take more than 4 cycles).
   B) Dose adjustments for hematology lab values:
      • For pts with normal counts at baseline (WBC > 3 x 10⁹/L, ANC > 1.5 x 10⁹/L, and
        platelets > 75 x 10⁹/L)
        | ANC Nadir (x 10⁹/L) | Platelet Nadir (x 10⁹/L) | % Dose Reduction in next cycle |
        |---------------------|--------------------------|--------------------------------|
        | < 0.5               | < 25K                    | 50%                           |
        | 0.5 – 1.5           | 25 – 50K                 | 33%                           |
        | > 1.5               | >50K                     | 0%                            |
      • For platelets with low counts at baseline (WBC < 3 x 10⁹/L, ANC < 1.5 x 10⁹/L, or
        platelets < 75 x 10⁹/L)
        | WBC or Plt Nadir % decrease from baseline | BM Biopsy Cellularity at Nadir (%) | % Dose Reduction in next cycle |
        |-------------------|--------------------------|--------------------------------|
        | 50 – 75           | 30 – 60                  | 15 – 30                       | < 15                          |
        | > 75              | 0%                       | 50%                           | 67%                           |
        |                   | 25%                      | 50%                           | 67%                           |
      • Exception: if there is a clear improvement in differentiation at the time of the next cycle,
        the previous dose should be continued
   C) Delayed recovery: if a 25% increase above the nadir is not seen by day 42, the patient
      should be treated with a 50% reduction in dose.
D) Dose adjustments based on renal function and electrolytes:

- If serum bicarbonate levels decrease to < 20 mEq/L without explanation, then the azacitidine dose should be reduced by 50% on the next cycle.
- If unexplained increases in BUN and creatinine occur, the next cycle should be delayed until values return to normal/baseline, and the next dose should be reduced by 50%

E) Vials should be reconstituted to form a 25 mg/mL suspension.

F) Azacitidine is administered as a subcutaneous injection. Doses greater than 4 mL (100 mg) should be divided equally into two syringes and given as two separate injections.

G) New injections should be given at least one inch from an old site. Drug should NOT be injected into areas where the site is tender, bruised, red, or hard.

H) Reconstituted drug is stable for 1 hour at room temperature (25° C) or for up to 8 hours under refrigeration (2° – 8° C). Refrigerated doses should be allowed to come to room temperature for 30 minutes prior to administration.

IV. TOXICITY

A) The most common adverse events requiring clinical intervention (interruption or discontinuation of therapy, dose reductions) are leukopenia, neutropenia, and thrombocytopenia. Myelosuppression appears to decrease with onset of clinical response.

B) The most common adverse reactions occurring in patients receiving subcutaneous injections of azacitidine are nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site erythema, constipation, neutropenia, and ecchymosis.

C) Other reported adverse effects include elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, and hepatic coma.

D) The following serious but infrequent (<5% occurrence) have been reported in clinical trials of IV or subcutaneous azacitidine:

**Blood and lymphatic system** – agranulocytosis, splenomegaly; **Cardiac** – atrial fibrillation, cardiac failure, congestive heart failure, cardiorespiratory arrest, congestive cardiomyopathy; **GI disorders** – diverticulitis, GI hemorrhage, melena, perirectal abscess; **Hepatobiliary** – cholecystitis; **Immune system** – anaphylactic shock, hypersensitivity; **Infection** – limb abscess, bacterial infection, blastomycosis, injection site infection, sepsis, *Klebsiella* sepsis, streptococcal pharyngitis, *Klebsiella* pneumonia, staphylococcal bacteremia, toxoplasmosis; **Musculoskeletal** – aggravated bone pain, muscle weakness, neck pain; **Neoplasms** – leukemia cutis; **Nervous system** – Convulsions, intracranial hemorrhage; **Renal/urinary** – hematuria, loin pain, renal failure; **Respiratory/Thoracic** – hemoptysis, lung infiltration, pneumonitis, respiratory distress; **Skin** – pyoderma gangrenosum, rash, skin induration.

V. CLINICAL MONITORING

A) CBC should be done as needed to monitor response and toxicity (at minimum, prior to each dosing cycle).

B) As azacitidine is potentially hepatotoxic in patients with severe pre–existing hepatic impairment, caution should be taken in patients with hepatic disease.

C) Patients with renal impairment should be closely monitored as azacitidine and its metabolites are primarily excreted by the kidneys.

D) Azacitidine may cause fetal harm. Women of childbearing potential should avoid becoming pregnant. Men should avoid fathering children while receiving azacitidine.
VI. DRUG INTERACTIONS

Drug interaction studies have not been conducted. Azacitidine may be metabolized by the liver; whether its metabolism is affected by microsomal enzyme inhibitors or inducers is not known. *In vitro* studies indicate that at concentrations of 1 to 100 microM, azacitidine does not induce CYP 1A2, 2C19, or 3A4/5.
CAPECITABINE
(XELODA®)

I. MECHANISM OF ACTION
Readily absorbed from the GI tract and converted in the liver by carboylesterase to 5′-deoxy-5′-fluorocytidine (5′-DFCR). This compound is readily taken up by tumor and normal tissue. The ratio of uptake in colon cancer tissue to adjacent normal tissue is 2.9 to 1. In cancerous tissue, it is converted to fluorouracil and then acts just like 5-FU.

II. PHARMACOKINETICS
A) Absorption – capecitabine levels peak in 1.5 hr but 5-FU levels take 2 hours to peak. Take with food or within 30 minutes of a meal.
B) Distribution–Protein binding is < than 60%; 35% to albumin
C) Metabolism and elimination–Extensive conversion to 5-FU. It is then cleared as inactive metabolites in the urine.
D) Dose modification for renal impairment:
   • CrCL > 51 mL/minute: No adjustment of initial dosage
   • CrCL 30 – 50 mL/minute: Reduce initial dose by 25%
   • CrCL < 30 mL/minute: Do NOT use
E) Dose modification for hepatic impairment: No starting dose adjustment is necessary, however carefully monitor patients. The agent has not been studied in patients with severe hepatic impairment.

III. DOSING AND ADMINISTRATION
Oral dose of 2500 mg/m² daily (divided into 2 doses) for 14 days then 7 days off. Repeat cycle every 21 days. Daily doses are divided into 2 doses 12 hours apart; take with water and at the end of a meal. Available as 150 mg and 500 mg tablets.

IV. TOXICITY (follow algorithm for dose modifications for toxicity)
A) GI– Diarrhea (57%). If pt has more than 2 stools in a day, then stop capecitabine immediately. Loperamide may help. Nausea/vomiting (30–50%, but low grade).
B) Dermatologic–hand–foot syndrome/palmar–plantar erythema (PPE) – incidence 57% and potentially serious. This is defined as painful erythema and swelling of the hands and feet that result in discomfort affecting daily activities. Grade 3 hand–and–foot syndrome is defined as moist desquamation, ulceration, blistering, and severe pain of the hands and feet that results in severe discomfort that causes the pt to be unable to work or perform normal daily activities. If Grade 2/3 hand–and–foot syndrome occurs, interrupt administration of capecitabine until the event resolves or decreases in intensity to Grade 1. Following Grade 3 hand–and–foot syndrome, decrease subsequent doses of capecitabine (see table below). A recent abstract presented at ASCO [Proc Am Soc Clin Oncol 2001;20:abstract 1565] demonstrated an advantage in prescribing vitamin B₆ to patients on capecitabine. Doses of greatest benefit were 200 – 300 mg PO daily. The median number of cycles to onset of PPE was 2.
<table>
<thead>
<tr>
<th>Toxicity NCIC Grades</th>
<th>During a course of therapy</th>
<th>Dose adjustment for next cycle (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>First appearance</td>
<td>Interrupt until resolved to Grade 0–1</td>
<td>100%</td>
</tr>
<tr>
<td>Second appearance</td>
<td>Interrupt until resolved to Grade 0–1</td>
<td>75%</td>
</tr>
<tr>
<td>Third appearance</td>
<td>Interrupt until resolved to Grade 0–1</td>
<td>50%</td>
</tr>
<tr>
<td>Fourth appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First appearance</td>
<td>Interrupt until resolved to Grade 0–1</td>
<td>75%</td>
</tr>
<tr>
<td>Second appearance</td>
<td>Interrupt until resolved to Grade 0–1</td>
<td>50%</td>
</tr>
<tr>
<td>Third appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
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<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First appearance</td>
<td>Interrupt until resolved to Grade 0–1</td>
<td>75%</td>
</tr>
<tr>
<td>Second appearance</td>
<td>Interrupt until resolved to Grade 0–1</td>
<td>50%</td>
</tr>
<tr>
<td>Third appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
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<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First appearance</td>
<td>Discontinue permanently, or if the MD deems it to be in the patients best interest, interrupt until resolved to grade 0–1</td>
<td>50%</td>
</tr>
</tbody>
</table>

Reference: Facts and Comparisons, 2006, St Louis, MO [Accessed 07/20/06].

C) Hematologic– neutropenia (26%), thrombocytopenia (24%), anemia (72%) and all three are generally mild, but lymphopenia (94%) may be serious and have half the patients with grade 3 or 4 toxicity.

D) Others–mucositis (24%), skin rash (37%), fatigue (41%), anorexia (23%), hyperbilirubinemia (22%).

E) Cardiac – angina–like chest pain, MI, dysrhythmias, cardiogenic shock, sudden death, and EKG changes (SEE 5–Fluorouracil section).

V. CLINICAL MONITORING:
A) Physical examination – oral cavity, skin. Evaluate for PPE.
B) CBC and differential.

VI. DRUG INTERACTIONS
Capecitabine is metabolized by the CYP 2C9 enzyme system, and care should be exercised when co-administering with other CYP 2C9 substrates.
A) Warfarin: Black box warning. Patients receiving concomitant capecitabine and oral coumarin–derivative anticoagulant therapy should have their anticoagulant response (INR or PT time) monitored frequently and adjusted accordingly. Drug interactions have been reported and typically occur within several days of initiation. This interaction may take up to several months to occur. These interactions occurred in patients with and without liver metastasis. Results in increased AUC and decreased CL. In a small study of 4 patients the maximum observed mean INR was increased by 91% with concomitant therapy.
B) Phenytoin: monitor phenytoin levels in patients taking capecitabine with phenytoin, as the dose of phenytoin may need to be reduced (phenytoin toxicity has been reported).
I. MECHANISM OF ACTION
   A) Cytarabine enters cells by carrier proteins and by diffusion. It is rapidly destroyed by enzymes (cytidine deaminases) in the tissue of the liver and gut. Cytarabine must first be activated by a series of intracellular enzymes (cytidine kinases).

   Cytarabine
   Deoxycytidine kinase
   Ara-CTP (triphosphorylated form) = competitive inhibitor of DNA polymerase

   B) Cytarabine acts similar to the nucleoside, cytidine
   C) Cytarabine acts in two very different ways, both of which stop DNA replication. First of all it inhibits DNA polymerase, the enzyme necessary for DNA chain elongation. Secondly, cytarabine gets incorporated into DNA leading to errors in replication, transcription and translation.
   D) Cytarabine is phase specific for the S phase.
   E) Resistance can be due to decreased concentrations of cytidine kinases, increased concentrations of cytidine deaminases, or decreased cellular transport.

II. PHARMACOKINETICS
   A) Distribution: Cytarabine distributes widely throughout body water and easily crosses into the CNS. Drug levels in CSF at high doses of cytarabine are adequate to treat CNS disease so that intrathecal therapy isn’t necessary.
   B) Metabolism: rapidly metabolized in the gut wall and the liver such that the t½ is only 7–20 minutes.
   C) Elimination: 70 – 80% of the metabolites formed are eliminated in the urine.
   D) Plasma levels achieved are proportional to dose up to 2000 mg/m²/dose and then rise more rapidly than an increase in dosage. Subcutaneous and intravenous administration yields similar plasma concentrations for the same dose.

III. DOSING AND ADMINISTRATION:
   Subcutaneously, intravenously (continuous infusion or intermittent infusions over 2 – 3 hours), or intrathecally. Intrathecal doses are 30 – 50 mg intrathecally and should be in minimum volume and preservative free.

IV. TOXICITY
   A) Cytarabine’s adverse effects are dependent upon dose and schedule. Standard Dose means 100 or 200 mg/m²/day given as a CIVI over several days. High dose means from 1 to 3 grams/m² given every 12 hr for several doses (e.g., 12) as a short (e.g., 3 hr) infusion. Do NOT give high dose as a continuous infusion = VERY toxic.
   B) Myelosuppression– A desirable adverse effect in the treatment of leukemia, it usually begins on day 7 and resolves by day 21–28.
   C) Gastrointestinal– Overall 40–60% of patients will have some GI complaint. With high-dose cytarabine, nausea 6–12 hours after a dose occurs universally and often leads to vomiting. Suggested antiemetic orders for high dose cytarabine: 5–HT₃RA orally 30 min before each dose of Ara-C. Dexamethasone 8 mg PO should also be given before each Ara-C dose. Diarrhea: 20–60%. Oral mucositis: 20 – 50%. Intrahepatic cholestasis with
elevations of SGOT, SGPT, and alkaline phosphatase occurs frequently but rarely necessitates stopping therapy. Ileus, abdominal pain, GI bleeding, and pancreatitis have also been noted.

D) Neurologic– Overall, 20% of patients have some cerebral or cerebellar signs. Onset in 3–12 days and lasting 3–7 days. Neurotoxicity is more common with higher doses, with continuous infusions of higher doses, in patients over age 50, and in patients with a creatinine clearance under 60 mL/min. Dose reduction should occur in this patient population [Reference: Smith GA, et al. J Clin Oncol 1997;15:833 – 9]. Signs and symptoms: slurred speech, unsteady handwriting, unsteady gait, ataxia, nystagmus, diplopia, tremor, dementia, and coma.

E) Ocular– Usually only a problem with high dose cytarabine. Conjunctivitis or keratitis in 25–80%, onset 4–8 days after treatment. Photophobia and excessive lacrimation. Ophthalmic dexamethasone (2 drops each eye q6h) will prevent or relieve the inflammation caused by cytarabine. Begin drops 12 hours prior to cytarabine. Discontinue dexamethasone 48 hours after last dose of cytarabine, but continue if symptoms persist.

F) Dermatologic– Skin rash in up to 75%. Palmar–plantar erythema (PPE) and neuropathy.

G) Pulmonary– 20% of patients may develop pulmonary edema or ARDS. Usually only a problem with high dose therapy, and can be minimized by avoid fluid overload status. Maintain strict control on patient’s weight during cytarabine administration.

V. CLINICAL MONITORING
A) Physical exam– oral cavity, rectal exam, urine output, eyes, skin, pulmonary exam, neuro exam with special attention to cerebellar function.
B) Labs – CBC with differential and platelets, LFT’s, serum creatinine, and BUN.
DECITABINE
(5-Aza-2’-Deoxycitidine, DACOGEN®)

I. MECHANISM OF ACTION
A) Decitabine is a cytosine analog
B) It causes hypomethylation/demethylation of DNA. It is incorporated into DNA during S phase and forms covalent adducts with DNA methyltransferase. The irreversible inhibition of this enzyme results in loss of methylation and is associated with differentiation. Demethylation may restore normal function to tumor-suppressor genes that are responsible for regulating cell differentiation and growth.
C) Decitabine is approximately 5–fold more potent an inhibitor of DNA methyltransferase than is azacitidine. It can induce differentiation of myeloid progenitors in vitro at lower doses than azacitidine.
D) At higher concentrations, it has direct cytotoxic effects.

II. PHARMACOKINETICS
A) From phase I studies, decitabine has a very short plasma half-life. Distribution half-life is $7 \pm 1$ minutes, and elimination half-life is $35 \pm 5$ minutes. The volume of distribution is approximately 4.6 L/kg.
B) Decitabine is rapidly inactivated by deamination by liver cytidine deaminase. Clearance is high, on the order of 126 mL/min/kg. Urinary excretion accounts for < 1% of the total administered dose.
C) Administration of 100 mg/m² IV over 3 hours results in plasma concentrations of 0.1 – 0.4 mcg/ml. Continuous infusions of 1 mg/kg/hour for 40 – 60 hours results in plasma concentrations of 0.43 – 0.76 mcg/ml. Steady-state plasma concentrations (Cₚₛ) on 1 mg/kg/hour is approximately 0.2 – 0.5 mcg/ml.
D) Cerebrospinal fluid concentrations are 14 – 21% of plasma concentrations at the end of a 36–hour infusion.

III. DOSAGE AND ADMINISTRATION
A) The optimal dose and schedule for this drug has not been determined.
B) In a study in patients with CML, patients received 100 mg/m² IV over 6 hours daily for 5 days every 4 to 8 weeks. Because of severe and prolonged myelosuppression, the starting dose was reduced to 75 mg/m², then to 50 mg/m²/dose. (Cancer 2003;98:522 – 8)
C) In a recent phase III trial in MDS patients, decitabine was dosed at 15 mg/m² IV over 3 hours q8hr x 9 doses and is the FDA approved dose. Recently a daily administration schedule (20 mg/m² IV daily for 5 days) was evaluated and produces similar responses to the FDA approved dosing.
D) In clinical trials, decitabine has been given as intermittent as well as continuous IV infusions
E) Vials of lyophilized powder must be stored at refrigerator temperature (2°–8°C)
F) Reconstitution of the powder results in a rapidly decomposing solution. Therefore, the solution should be prepared using cold diluent and stored in a refrigerator after preparation. Prepared doses can be kept for up to 10 hours in a refrigerator, and must be infused within 3 hours after storage under refrigeration for up to 10 hours.
IV. TOXICITY
A) In clinical trials, the most common adverse effects are neutropenia, infectious episodes, and nausea, vomiting, diarrhea, and fatigue.
B) Serious but infrequent adverse effects that have been reported in patients treated in clinical trials so far include: seizures, renal failure, atrial fibrillation, myocardial infarction, and pulmonary embolism.
C) Myelosuppression appears to be significant and is dose-related.
D) Decitabine is teratogenic in animal models.

V. CLINICAL MONITORING CBC with differential, LFT’s, and serum creatinine/BUN.

VI. DRUG INTERACTIONS
Drug interaction studied with decitabine have not yet been conducted. In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce CYP450 enzymes. In vitro metabolism studies have suggested that decitabine is not a substrate for the human liver CYP450 enzymes. As plasma protein binding of decitabine is negligible (< 1%), interactions due to displacement of highly protein bound drugs from plasma proteins is not expected.

Full prescribing information, including clinical trial information, safety, dosing, drug–drug interactions and contraindications is available at www.fda.gov/cder/foi/label/2006/021790lbl.pdf.
5-FLUOROURACIL (5-FU)

I. MECHANISM OF ACTION
   A) A cell-cycle specific antimetabolite whose activity is dependent upon concentration and time of exposure.
   B) Requires activation by intracellular enzymes before acting.
   C) Three mechanisms of 5-FU’s action. The 1st is incorporation into RNA to form phony RNA, which synthesizes proteins incorrectly. Secondly, 5-FU can lead to errors in replication, transcription and translation. Lastly, it binds to the enzyme thymidylate synthetase, which is essential for DNA synthesis. Binding to thymidylate synthetase requires an active form of folic acid, which is why calcium leucovorin is sometimes given with 5-FU.

   ![Liver Diagram]

   INTRACELLULAR

   Active Metabolites (5-FUTP)
   - Act as false substrates
   - Incorporates into DNA
   - Inhibits Thymidylate Synthetase (5-FdUMP)

   Defective RNA synthesis
   Inhibits DNA Synthesis

II. PHARMACOKINETICS
   Metabolism and Elimination– rapidly cleared from blood, extensively by enzymes in the lungs and liver. The t½ is 6–20 minutes. Ninety percent of a dose is metabolized and 5% excreted unchanged in the urine.

III. DOSAGE AND ADMINISTRATION
   5-Fluorouracil is given as an IV push or as a continuous infusion. It has also been given IA, IP, and topically. Administration into the hepatic portal vein has been used for liver metastasis.
IV. TOXICITY
A) Gastrointestinal– Nausea and vomiting in 30%. Mucositis/stomatitis all along the GI track can be manifested as a dry mouth, erythema, white patches, ulcers, retrosternal burning, diarrhea, and proctitis. Mucositis/stomatitis is more common with continuous infusion administration than IV push.
B) Myelosuppression– mostly with IV push.
C) Thrombosis
D) Dermatologic– alopecia, nail discoloration, hyperpigmentation, radiosensitization, photosensitivity, serpentine vein discoloration, palmar–plantar dermatitis. Occurs most commonly with bolus and CIVI administration.
E) Neurologic– Somnolence, ataxia
F) Cardiovascular– chest pain, EKG changes, myocardial ischemia. Anginal pain imitates vasospastic angina. Responds to nitrates, calcium channel blockers, and beta–blockers. Occurs with both bolus and CIVI administration, although appears to be more common with CIVI administration (as well as in those regimens that contain leucovorin).
G. Ocular– blepharitis, conjunctivitis, excessive lacrimation.

V. CLINICAL MONITORING
A) Labs– LFT’s, CBC with differential and platelets.
B) EKG, CXR, and KUB
C) Physical exam– oral cavity, rectum, lungs, abdomen, skin especially on the hands, arms, feet, legs, and face; neurological exam; cardiac exam; ocular exam.
I. MECHANISM OF ACTION

Gemcitabine

\[ \text{Triphosphorylated by deoxycytidine kinase} \]

Gemcitabine Triphosphate

\[ \text{Inhibits DNA polymerase activity} \]

A) Initially triphosphorylated by deoxycytidine kinase
B) Inhibits DNA synthesis by competitively inhibiting DNA polymerase
C) Incorporated into DNA and leads to impaired DNA chain elongation. RNA incorporation has also been observed.
D) The diphosphorylated form is an inhibitor of ribonucleotide reductase.
E) Compared to cytarabine, gemcitabine has less affinity for cytidine deamination and better membrane permeability. Cytotoxicity may be proportional to the extent of DNA incorporation.
F) S-phase specific

II. PHARMACOKINETICS

A) Distributes into body water. Distribution increases with longer infusions.
B) Metabolized in plasma to inactive substances eliminated in the urine. Only 5% of a dose is eliminated unchanged in the urine. Clearance is independent of dose or duration of infusion; however, half-life increases with longer infusion duration because of the enlarged volume of distribution.

III. DOSAGE AND ADMINISTRATION

Typically administered as a weekly 30-minute infusion at a dose of 1000 mg/m². Begin with weekly for 7 then 1-week rest then weekly 3 out of every 4 weeks. Fixed-dose rate (FDR) infusion maximizes intracellular concentrations by administering at a rate of 10 mg/m²/minute.

IV. TOXICITY

A) Dose limiting neutropenia (6–51%) and thrombocytopenia (1–51%); not cumulative.
B) Nausea/vomiting: usually mild–moderate (69% patients) and severe in < 15% patients.
C) Transient fevers.
D) Flu-like symptoms.
E) Chemical hepatitis.
F) Rashes in 50% of patients are macular, erythematous, and pruritic.
G) Pneumonitis and exacerbation of radiation i.e., radiation recall.
PURINE ANTAGONISTS

CHLORODEOXYADENOSINE – CLADRIBINE (2–CDA)
(LEUSTATIN®)

I. MECHANISM OF ACTION
Triphosphorylated form inhibits DNA polymerase, DNA ligase, and ribonucleotide reductase. Causes accumulation of DNA strand breaks and increased utilization of ATP, leading to cell death. Selective for lymphocytes. Acts on resting and dividing cells. Also destroys monocytes and impairs IL–6 production which may explain why thrombocytopenia occurs with 2–CDA therapy. Resistance may be due to excessive deoxycytidine concentrations, low deoxycytidine kinase activity, or high deoxynucleotide activity.

II. PHARMACOKINETICS
A) Absorption–has been investigated as oral agent but is not currently feasible.
B) Distribution and metabolism – is rapid; distribution half–life is 30 minutes. Terminal half–life is 7 hours.
C) Elimination – probably renal. Specific guidelines for dose adjustment in renal impairment are not available. Suggests dose modification not necessary.

III. DOSAGE AND ADMINISTRATION
Given as a continuous infusion over 7 days at a dose of 0.09 mg/kg/day in 500 mL NS or 0.12 mg/kg/day over two hours for 5 days. Incompatible with dextrose. 2–CDA can also be administered as a subcutaneous injection.

IV. TOXICITY
A) Neutropenia – Occurs in over 50% of patients. Recovery by day 28.
B) Thrombocytopenia – 30–100% of patients.
C) Lymphopenia – CD4 and CD8 counts may be depressed for up to 6 months. Opportunistic infections are not uncommon.
CLOFARABINE
(CLOLAR®)

I. MECHANISM OF ACTION
Clofarabine acts to decrease DNA synthesis as well as inhibit DNA repair. Clofarabine is metabolized intracellularly to the active triphosphate metabolite. The drug decreases cellular deoxynucleotide triphosphate pools by inhibiting ribonucleotide reductase. This also serves to terminate DNA chain elongation. Clofarabine has demonstrated the ability to incorporate into the DNA chain by inhibition of DNA polymerases. It is by this mechanism that the drug has the ability to inhibit DNA repair.

II. PHARMACOKINETICS
The population pharmacokinetics of clofarabine has been studied in pediatric patients with relapsed or refractory ALL and AML. Clofarabine was 47% bound to plasma proteins, predominantly albumin. Volume of distribution and systemic clearance were 172 L/m² and 28.8 L/hour/m², respectively. 24-hour urine collection indicated that 49 – 60% of the dose is excreted unchanged in the urine. In vitro studies have shown very limited metabolism; elimination by non–renal routes remains unknown. The terminal half–life is estimated to be 5.2 hours. The PK of clofarabine has not been studied in patients with renal or hepatic dysfunction.

III. DOSAGE AND ADMINISTRATION
Clofarabine is available as a 1 mg/mL solution, supplied in 20 mL vials. The recommended pediatric dose for ALL is 52 mg/m² administered as an IV infusion over 2 hours. It is administered daily for 5 consecutive days. Treatment cycles are repeated every 2 – 6 weeks following return to baseline organ function.

The dosage for adults for acute leukemia in phase II studies is 40 mg/m² administered as an IV infusion over 1 hour. The dose is administered daily for 5 days. A smaller dose has been used for 2 – 3 courses in adult patients for consolidation.

IV. TOXICITY
The most common adverse events following clofarabine administration are GI including nausea, vomiting and diarrhea; hematological including anemia, leukopenia, thrombocytopenia, neutropenia, febrile neutropenia and infection.

In pediatric patients, hepatobiliary toxicity consisting of grade 3 or 4 elevations in transaminases as well as bilirubin was found to be the dose limiting toxicity. Elevations in transaminases appear to be transient with the majority occurring within 1 week of treatment and returning to < Grade 2 within several days. Hyperbilirubinemia appears to be more common and more persistent with a median time of 6 days for elevations to return to less than Grade 2.

Systemic inflammatory response syndrome (SIRS) or capillary leak syndrome is another adverse event associated with the administration of clofarabine in pediatric patients. Signs and symptoms of SIRS such as tachypnea, tachycardia, hypotension, and pulmonary edema have occurred in 4 pediatric patients overall. The use of prophylactic steroids (100 mg/m² hydrocortisone on days 1–3) has been proposed as a means of preventing this event. If SIRS does occur, the drug should be discontinued immediately. Once the patient has returned to baseline they can be rechallenged at a lower dose.
Cardiovascular toxicities, including tachycardia, pericardial infusion and left ventricular systolic dysfunction associated with clofarabine administration were also noted.

Precautions include insuring adequate hydration of patients receiving clofarabine to prevent dehydration that may occur due to vomiting and diarrhea as well as to reduce the effects of tumor lysis syndrome. Concomitant medications that are nephro- or hepatotoxic should be avoided due to the renal elimination of the drug and the increased incidence of hepatotoxicity associated with it.

V. DRUG INTERACTIONS
No clinical drug–drug interaction studies have been conducted; however, based on the results of in vitro studies, CYP450 inhibitors and inducers are not likely to have an affect on the metabolism of clofarabine. The effect of clofarabine on substrates of CYP450 enzymes is not known.
FLUDARABINE
(FLUDARA®)

I. MECHANISM OF ACTION
Fludarabine is a prodrug that crosses cell membranes by carrier mediated transport, is triphosphorylated, and then binds to DNA polymerase, ribonucleotide reductase, DNA ligase, and DNA primase. DNA deletions and mutations occur. Fludarabine also is a DNA chain terminator by incorporation into DNA. DNA synthesis is inhibited. Active in B and T cells. Besides being an antitumor agent against low-grade lymphoid malignancies, it also has immunosuppressant activity and is incorporated into preparative regimens for non-myeloablative allogeneic BMT. Resistance is due to inability to phosphorylate the molecule.

II. PHARMACOKINETICS
A) Absorption—80–100% orally bioavailable (not commercially available as an oral agent).
B) Distribution—wide and bound to body tissues
C) Metabolism—minimal
D) Elimination—Extensive renal elimination (approximately 40% dose). Because of empiric evidence linking fludarabine to CNS toxicity in patients with renal insufficiency, the dose should be reduced. Manufacturer recommendations are: patients with moderate impairment of renal function (creatinine clearance 30–70 mL/min/1.73 m²) should have the fludarabine dose reduced by 20% and be monitored closely. Fludarabine is not recommended for patients with severely impaired renal function (creatinine clearance less than 30 mL/min/1.73 m²). See guidelines and recommendations for dosing antineoplastic agents in renal failure (miscellaneous section).

III. DOSAGE AND ADMINISTRATION
In 100 mL of NS or D₅W over 30 min and given at a dose of 25 – 30 mg/m²/day each day for 3–5 days each month. Longer courses of fludarabine using higher doses are used in BMT preparative regimens, e.g., 30mg/m² for 6 days; shorter courses are often used when fludarabine is prescribed in combination with other cytotoxics.
Dose modification in renal impairment: The total body clearance of 2–fluoro–ara–A is directly correlated with creatinine clearance. In fact, the renal pathway represents about 40% of the total body clearance of fludarabine. For this reason, patients with moderate impairment of renal function (creatinine clearance 30 –70 mL/min/1.73 m²) should have the fludarabine dose reduced by 20% and be monitored closely. Fludarabine is not recommended for patients with severely impaired renal function (creatinine clearance less than 30 mL/min/1.73 m²). See guidelines and recommendations for dosing antineoplastic agents in renal failure (miscellaneous section).
IV. TOXICITY

A) Neutropenia—in 59% of patients with a median nadir by day 13 but recovery is delayed until day 37 in some cases.
B) Thrombocytopenia: 25% of patients. Recovery can again be delayed.
C) Infections can occur in about half the patients and may involve opportunistic organisms
D) Emesis: 36% of patients. Does not require 5HT3 antiemetics, use prochlorperazine, promethazine or metoclopramide.
E) Fever (60%)
H) Hemolytic anemia
I. MECHANISM OF ACTION
A) Phosphorylated and incorporated into RNA and DNA or inhibition of purine synthesis
B) Can be metabolized by xanthine oxidase so that allopurinol will enhance mercaptopurine activity. Methotrexate is a weak xanthine oxidase inhibitor.
C) A third pathway is catabolism by thiopurine methyltransferase to methylmercaptopurine. TPMT production demonstrates genetic polymorphism and lack of TPMT can enhance tumor activity or host toxicity. Overproduction could be a source of resistance.

\[
\begin{align*}
6\text{-MP} & \rightarrow 6\text{MP ribose phosphate} \rightarrow \text{incorporation into DNA + RNA} \\
\text{Xanthine Oxidase} & \\
6\text{-thioxanthine} & \rightarrow \text{Allopurinol Inhibits} \rightarrow \uparrow 6\text{-MP} \\
\text{Xanthine Oxidase} & \\
6\text{-Thiouric acid} & \\
\end{align*}
\]

REDUCE THE DOSE OF 6-MP BY 50 – 75% WHEN ADMINISTERING WITH ALLOPURINOL.

II. PHARMACOKINETICS
A) Absorption – Peak concentrations in two hours. Bioavailability of mercaptopurine is only 16% because of intestinal wall and liver xanthine oxidase activity. Allopurinol increases bioavailability by 5 fold.
B) Distribution – poor CNS penetration.
C) Elimination – metabolism by xanthine oxidase and TPMT.

III. DOSAGE AND ADMINISTRATION
2.5 to 5 mg/kg/day orally in 2–3 doses daily. Round dose to the nearest 25–mg (half tab). Available as a scored 50 mg tablet. Take on an empty stomach.
Dose modification in renal impairment: Dosage should be modified depending on clinical response and degree of renal impairment, but no quantitative dosage recommendations are available. The following guidelines have been suggested:
- CrCL 50—80 mL/min: modify dosage interval to every 24—36 hours.
- CrCL 10—50 mL/min: modify dosage interval to every 48 hours.
- CrCL < 10 mL/min: no quantitative dosage recommendations are available.
Reference: Clinical Pharmacology Online, Accessed 03/29/05.

IV. TOXICITY
A) Myelosuppression – 1 – 4 weeks from start of therapy (nadir day 7, recovery day 14).
B) Mild emesis.
C) Cholestatic jaundice.
D) Elevated transaminases.
V. CLINICAL MONITORING:
Monitoring of serum transaminase, alkaline phosphatase and bilirubin levels may allow early detection of hepatotoxicity. Monitor weekly when beginning therapy and monthly thereafter.

VI. DRUG INTERACTIONS:
When allopurinol is administered concomitantly with mercaptopurine, reduce mercaptopurine to a 1/3 to 1/4 of the usual dose (i.e., a 67% to 75% dose REDUCTION). Failure to observe this dosage reduction will delay catabolism of mercaptopurine and increase likelihood of severe toxicity. Trimethoprim/Sulfamethoxazole may also increase serum concentrations of mercaptopurine and lead to greater hematological toxicity.
NELARABINE (ARA–G; COMPOUND 506U78)
(ARRANON®)

I. MECHANISM OF ACTION
Nelarabine is a prodrug of the deoxyguanosine derivative ara–G. Nelarabine is demethylated by adenosine deaminase (ADA) to form ara–G. Ara–G is in turn phosphorylated by cellular deoxycytidine kinase and deoxyguanosine kinase to ara–GMP, which on subsequent phosphorylation is converted into active ara–GTP. Ara–GTP accumulates in vitro to significantly higher levels and for longer duration in T–cells than in other type of cells, including B–cells. Accumulation of ara–GTP in leukemia blasts allows for preferential incorporation of ara–GTP into deoxyribonucleic acid leading to inhibition of DNA synthesis and resultant cell death.

II. PHARMACOKINETICS
The pharmacokinetics of nelarabine have been evaluated in children and adults with refractory hematologic malignancies. The maximum concentration (Cmax) of nelarabine occurred at the end of the infusion. The nelarabine Cmax and area under the curve from time zero to infinity were proportional to the dose over the dose range of 5–75 mg/kg. Large variability in the CL and Vd (Vss) of nelarabine was seen in children (n = 20) and adults (n = 44). The harmonic mean half–life (t1/2) values of nelarabine in pediatric and adult patients were 14.1 and 16.5 minutes, respectively. In most studies, nelarabine was administered as a one–hour intravenous infusion. The consistent conversion of nelarabine to ara–G is required to produce reliable, effective ara–G concentrations. As 1 mol of ara–G is produced from 1 mol of nelarabine and the renal elimination of nelarabine is minimal, the elimination rate of nelarabine represents the formation rate of ara–G. Thus, in one hour, approximately 94% of nelarabine is converted to ara–G. Also, the formation of ara–G in the presence of fludarabine would not be expected to be altered. The Cmax of ara–G typically occurs at the end of the infusion of nelarabine and is proportional to the dose of nelarabine. The AUC of ara–G is also proportional to the nelarabine dose. Concentrations of ara–G decline monoexponentially with time. The harmonic mean t1/2 values of ara–G in children and adults are 2.1 and 3 hours, respectively. The longer t1/2 of ara–G in adults is related to a lower clearance of ara–G in adults. The pharmacokinetics of ara–G were similar on days 2 and 5 of a 5–day course, indicating that ara–G did not accumulate during the treatment regimen.

III. DOSAGE AND ADMINISTRATION
Nelarabine is available as a 5 mg/mL clear colorless solution for injection.
- The recommended adult dose is 1500 mg/m² administered intravenously over 2 hours on days 1, 3, and 5. Repeat cycle every 21 days.
- The recommended pediatric dose is 650 mg/m² administered IV over 1 hour daily for 5 consecutive days, repeated every 21 days.

In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity, or the patient became a candidate for a HSCT.
Renal impairment: Nelarabine and ara-G PK have not specifically been evaluated in renal impairment or hemodialysis patients. The kidney to a small extent (~5 – 10% of a dose) excretes Nelarabine. The kidney to a greater extent (20–30% of the administered nelarabine dose) excretes ara-G. In a PK/PD cross–study analysis with a limited number of renally impaired patients (n = 2; CrCL < 50 mL/min), BL calculated CrCL was a significant predictor of ara–G apparent clearance. Ara–G CL was 7% lower in patients with mild renal impairment compared with those with normal renal function. Because the risk of toxicity may be greater in patients with impaired renal function, monitor this population very closely.

IV. TOXICITY

A) Pediatrics: Hematological toxicity was common. Grade 3/4 anemia occurred in 20%/14% respectively. Neutropenia: Grade 3/4 in 14%/49% patients respectively. Thrombocytopenia: Grade 3 in 37% patients and Grade 4+ in 22% patients. The most frequent non–hematologic Grade 3 events were increased bilirubin (6%) and peripheral neurological disorders (7%). The most common Grade 4 toxicity was seizures (6%).

B) Adults: Hematological toxicity was common. Grade 3 anemia occurred in 45% patient's and Grade 4+ in 10% of patients. Neutropenia: Grade 3 in 17% and Grade 4+ in 62% patients. Thrombocytopenia: Grade 3/4 in 27%/32% patients. The most frequent non–hematologic Grade 3 events were lowered consciousness (11%) and febrile neutropenia (9%). The most common Grade 4 toxicity was lowered consciousness (3%).

C) Neurotoxicity: neurological adverse events were a focus during the development of nelarabine. Early Phase II trials demonstrated severe neurological toxicity necessitating a decrease in the recommended doses for pediatric and adult patients, and the implementation of guidance for discontinuation of treatment for certain grade 2 or greater neurological toxicities that persist or worsen. Among 103 adult patients who received 1500mg/m2 doses, the most frequent nervous system AE was: lowered consciousness (63%), dizziness (21%), peripheral neurological disorders (18%), hypoesthesia (177%), paresthesia (15%) and HA (15%). Neurological SAE's occurred in 8% patients. Among this population 1% were fatal, 23% did not resolve, 47% resolved and 28% the outcome is unknown. Similar proportions were noted for the overall population.

V. CLINICAL MONITORING
CBC and differential; neurological status; liver function tests. Appropriate monitoring for tumor lysis syndrome should occur. Nelarabine should be discontinued at the first sign of neurological events using NCI CTC criteria of grade 2 or greater. Dosage may be delayed for other toxicity including hematological toxicity.

VI. DRUG INTERACTIONS
In a combination study of nelarabine and fludarabine, no effect on nelarabine, ara–G, or intracellular ara–GTP PK was observed after fludarabine administration on Day 3. Nelarabine and ara–G were neither substrates nor inhibitors of \( p \)-glycoprotein, nor did they inhibit major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Protein binding in human plasma for nelarabine and ara–G was low (<25%) and independent of concentration. These findings suggest that the potential for drug interactions via these mechanisms is low.
PENTOSTATIN (2′-deoxycoformycin)  
(NIPENT®)

I. MECHANISM OF ACTION
Pentostatin is an irreversible inhibitor of the enzyme adenosine deaminase (ADA). Pentostatin blocks the conversion of adenosine to inosine by the enzyme adenosine deaminase. This results in cellular accumulation of adenosine or deoxyadenosine, which appears to be selectively toxic to certain types of T-lymphocytes. By inhibiting ADA, pentostatin allows accumulation of deoxyadenosine triphosphate. Cells that are most susceptible to the effects of ADA inhibition are those with a relatively highly activity ratio of deoxynucleotide kinases (phosphorylating enzymes) to 5'-nucleotidase, such as seen in T-lymphocytes. Suspected mechanisms of action include accumulation of deoxyadenosine triphosphate, leading to inhibition of ribonucleotide reductase, incorporation of triphosphate derivatives of pentostatin into DNA, and interference with nicotinamide adenine nucleotide formation.

II. PHARMACOKINETICS
Approximately 50 – 96% of a dose is eliminated via the kidneys in the urine within 24 hours. Doses must be modified for renal impairment as follows:
- CrCL < 30 mL/minute: omit the dose or use with extreme caution
- CrCL 30 – 60 mL/minute: reduce dose by 50%
Reference: Clinical Pharmacology Online, Accessed 03/29/05.

III. DOSAGE AND ADMINISTRATION
Typical doses are 2 – 4 mg/m². Hydrate with 500 to 1000 mL 5% dextrose in 0.5 normal saline or equivalent before pentostatin administration. Administer an additional 500 mL 5% dextrose or equivalent after pentostatin is given. Administered by IV bolus over 3 – 5 minutes in D₃W or NS.

IV. TOXICITY
A) Myelosuppression – primarily neutropenia, lymphocytopenia, thrombocytopenia. Recovery from lymphocytopenia may be prolonged and incomplete.
B) Rashes.
C) Renal toxicity: Renal toxicity was observed at higher doses in early studies; however, in patients treated at the recommended dose, elevations in serum creatinine usually were minor and reversible. There were some patients who began treatment with normal renal function who had evidence of mild to moderate toxicity at a final assessment.
THIOGUANINE
(TABLOID®)

I. MECHANISM OF ACTION
   Phosphorylated and incorporated into RNA and DNA

II. PHARMACOKINETICS
   A) Absorption– Peak concentration in 10–12 hours, but overall bioavailability is weak.
   B) Distribution– poor CNS penetration
   C) Elimination– methylation and urinary elimination

III. ADMINISTRATION
   2 – 2.5 mg/kg/day rounded to the nearest 20 mg (half tabs). Available as a 40 mg tablet.
   Dose modification is not required in renal impairment.

IV. TOXICITY
   A) Myelosuppression.
   B) Mild emesis.
   C) Cholestatic jaundice, veno–occlusive disease.

V. CLINICAL MONITORING
   CBC with differential monthly
   LFT’s: monthly

VI. DRUG INTERACTIONS
   There is in vitro evidence that aminosalicylate derivatives (e.g., balsalazide, olsalazine, mesalamine, 5–ASA or sulfasalazine) inhibit the enzyme thiopurine methyltransferase (TPMT). Inhibition of TPMT in patients who are receiving thioguanine, 6–TG, has resulted in increased sensitivity to myelosuppressive effects and rapid bone marrow suppression following the initiation of thioguanine therapy. Therefore, 5–aminosalicylates should be administered with caution to patients receiving concurrent thioguanine therapy [Reference: Clinical Pharmacology Online].
RIBONUCLEOTIDE REDUCTASE INHIBITORS

HYDROXYUREA
(HYDREA®)

I. MECHANISM OF ACTION
A) Blocks ribonucleotide reductase. Impairs conversion of ribonucleotides to deoxyribonucleotides. Requires a nonheme iron cofactor.
B) Impairs thymidine incorporation into DNA.
C) Impairs B₁₂ binding to transcobalamin II.
D) S-phase specific.
E) Resistance is due to increased ribonucleotide assembly.

II. PHARMACOKINETICS
A) Well absorbed.
B) Crosses the blood–brain barrier. Plasma to CSF ratio is 2:1 up to 4:1.
C) Distributes well into pleural effusions and ascites.
D) Cleared by the liver to urea and carbon dioxide.

III. DOSAGE AND ADMINISTRATION
A) Available as 200 mg, 300 mg, 500 mg capsules and 1000 mg tablets.
B) Capsules can be opened into a glass of water and consumed.
C) Dose on lean body weight.
D) For CML: Begin at 10 – 50 mg/kg and continue until the WBC reaches 5 x 10⁹/L or the platelet count falls below 100 x 10⁹/L; can start at higher dose i.e., 75 mg/kg if WBC is greater than 100 x 10⁹/L.
E) Sickle cell disease: 15 mg/kg PO once daily. If blood counts are in an 'acceptable' range, the dosage may be increased by 5 mg/kg/day PO every 12 weeks until a maximum tolerated dose or 35 mg/kg/day PO is reached. If blood counts are between the 'acceptable' and 'toxic' range, the dose is not increased. If blood counts are considered 'toxic,' hydroxyurea should be discontinued until hematologic recovery. Treatment can then be resumed after reducing the dose by 2.5 mg/kg/day PO from the dose associated with hematologic toxicity. Hydroxyurea may then be titrated up or down, every 12 weeks in 2.5 mg/kg/day increments, until the patient is at a stable dose that does not result in hematologic toxicity for 24 weeks. Any dosage on which a patient develops hematologic toxicity twice should not be tried again [Reference: Clinical Pharmacology Online].

IV. TOXICITY
A) Neutropenia is dose related. Less commonly observed are thrombocytopenia and anemia (macrocytic, Vitamin B₁₂ deficiency).
B) Dose–related emesis, diarrhea, and mucositis.
C) Dermatologic: cutaneous vasculitis toxicities, including vasculitic ulcerations and gangrene in patients with myeloproliferative disorders during hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitis ulcers reported in patients with myeloproliferative disease, hydroxyurea should be discontinued if vasculitis ulcerations develop and alternative cytoreductive agents should be initiated. Hydroxyurea can cause radiation recall.