ANTI-METABOLITES

Folate Antagonists: MTX, Pemetrexed, Raltitrexed
Pyrimidine Analogue: 5-FU, FUDR, Capecitabine, Gemcitabine
Purine Analogue: 6-MP, 6-TG, Cytosine Arabinoside, Fludarabine , Cladribine, Pentostatin
Others: Hydroxyurea

Methotrexate

Chemical nature: Anti-metabolite
Folate antagonist
Cell-cycle specific (acts in S-phase)

Mechanism of action: Activated to its active metabolite in the liver & cells, MTX is an inhibitor of the Dihydrofolate Reductase (DHFR) enzyme, which catalyses a reaction in which reduced folates are produced, which are essential for the biosynthesis of both purines and pyrimidines (thymidine). Thus MTX inhibits nucleic acid synthesis and ultimately leads to apoptosis.

Mechanism of resistance: (1) Reduced affinity of DHFR for MTX
(2) Increased cellular concentration of DHFR
(3) Reduced cellular entry of MTX

Pharmacokinetics: Oral absorption is erratic while parenteral absorption is 100%.
Widely distributed in the body-at low doses, only 5-10% concentration is attained in the CSF but at high doses, there is therapeutic concentration. Avidly enters third space collections (pleural effusion/ascites).
Metabolised in the liver and in cells to its active pulyglutamated form by the enzyme FPGS.
Excreted mainly via the kidney-80 to 90% is excreted unchanged within 24 hours.

Interactions: Drugs which retard the metabolism of MTX and lead to increase toxicity are NSAIDs and beta-lactam antibiotics.
Drugs which reverses the action of MTX is Leucovorin (Folinic Acid) .
Drug which antagonizes the action of MTX is L-Asparaginase.
Drugs which are potentiated by MTX are 5-FU and Warfarin.

Toxicities: (1) Bone marrow depression (WBC nadir at 4-7 days) (Dose-limiting)
(2) Mucositis, nausea & vomiting (May be dose-limiting)
(3) Renal failure
(4) Interstitial lung disease
(5) Neurotoxicity (especially after IT or high dose systemic therapy)-both acute & chronic forms are seen
(6) Skin rash, photosensitivity and radiation recall phenomenon.

(7) Menstrual irregularities, abortion and fetal death.

Routes of administration: Oral/IM/IV/IT

Dose: Low dose=10-50 mg/m^2 IV every 3-4 weeks

Intermediate dose=100-500 mg/m^2 IV every 2-3 weeks

High dose=1-12 gm/m^2 IV over 3/24 hours every 1-3weeks

Intra-thecal=10-15 mg/m^2 twice weekly until CNS is clear , then weekly for 2-6 weeks , then monthly.

Special points regarding administration:

(1) With HD MTX, hydration before, during and after the drug must be done, along with alkalization of urine. Blood levels of the drug must be measured daily, starting 24 hours after the administration. Leucovorin rescue is essential starting 24 hours after MTX administration until the blood level of MTX has dropped below dangerous levels. Leucovorin is commonly given in doses of 10 mg/m^2 IV/IM/PO every 6 hours until the level of MTC is below $5x10^{-8}$ M-commonly around 10-12 doses are required. Leucovorin is converted to N^5,N^{10}tetrahydrofolate, a reduced folate which donates methyl groups in a crucial reaction of DNA synthesis, which is catalysed by Thymidine synthase-this product is normally unavailable after HD MTX and Leucovorin is thus a rescue source-thus, given after 24 hours of HD MTX, it allows continuation of DNA synthesis in normal cells, without interfering with the cytotoxic effect of the drug on rapidly-dividing cells, such as tumor cells, within the first 24 hours.
(2) With IT MTX, preservative-free solution must be used.
(3) MTX should be used with caution in patients of renal dysfunction. Blood levels and creatinine clearance should be monitored during therapy.
(4) Folic acid supplements must be stopped before starting therapy otherwise effect will be compromised

Indications:

(1) Osteosarcoma
(2) Breast cancer
(3) Ca. Urinary Bladder
(4) Gestational Trophoblastic Neoplasia
(5) Non-neoplastic-in chronic connective tissue diseases (eg RA,SLE)
(6) ALL-for prophylaxis and treatment of CNS leukemia
(7) Primary CNS Lymphoma
(8) Head an Neck cancer

Pemetrexed

Chemical nature: Anti-metabolite
Folate antagonist
Cell-cycle specific (acts in S-phase)

Mechanism of action: Activated to its active metabolite in the liver by polyglutamation, Pemetrexed is an a multi-targetted folate anatagonist-it is an inhibitor of the enzymes Thymidilate Synthetase (TS) and Dihydrofolate Reductase (DHFR)-the latter catalyses a reaction in which reduced folates are produced, which are essential for the biosynthesis of both purines and pyrimidines (thymidine). Thus Pemetrexed inhibits nucleic acid synthesis and ultimately leads to apoptosis.

Mechanism of resistance: (1) Reduced affinity of TS for Pemetrexed
(2) Reduced cellular entry of Pemetrexed

Pharmacokinetics:

After IV administration,it is metabolised in the liver and in cells to its active pulyglutamated form by the enzyme FPGS.

Excreted mainly via the kidney- 90% is excreted unchanged within 24 hours.

Interactions: Drugs which retard the metabolism of Pemetrexed and lead to increase toxicity are NSAIDs and beta-lactam antibiotics.

Drugs which reverses the action of Pemetrexed is Leucovorin (Folinic Acid) .

Drug which antagonizes the action of Pemetrexed is L-Asparaginase.

Drugs which are potentiated by Pemetrexed are 5-FU and Warfarin.

Toxicities: (1) Bone marrow depression (Dose-limiting)
(2) Mucositis, nausea & vomiting (May be dose-limiting)
(3) Renal failure
(4) Interstitial lung disease
(5) Transient elevation of liver transaminases
(6) Skin rash (hand-foot syndrome)
(7) Fatigue

Routes of administration: IVonly

Dose: Alone=600 mg/m^2 IV every 3 weeks
With CDDP=500 mg/m^2 IV every 3 weeks

Special points regarding administration:

(1) Use with caution in patients with renal dysfunction
(2) Use folic acid and vit. B12 supplementation to reduce incidence of severe toxicity
(3) Stop Aspirin and NSAIDs at least 2 days before starting therapy.

Indications:

(1) Mesothelioma-1st line therapy in combination with CDDP
(2) NSCLC-2nd line therapy
(3) Ca. Breast
(4) Ca. Urinary Bladder
(5) CRC
(6) Ca. Pancreas

Raltitrexed

Chemical nature: Anti-metabolite
Folate antagonist
Cell-cycle specific (acts in S-phase)

Mechanism of action: Activated to its active metabolite in the liver by polyglutamation, Raltitrexed is an inhibitor of the enzyme Thymidilate Synthetase (TS) -this inhibits nucleic acid synthesis and ultimately leads to apoptosis.

Mechanism of resistance: (1) Reduced affinity of TS for Raltitrexed
(2) Reduced cellular entry of Raltitrexed

Pharmacokinetics:
After IV administration,it is metabolised in the liver and in cells to its active polyglutamated form by the enzyme FPGS.
Excreted mainly via the kidney.

Interactions: Drugs which retard the metabolism of Raltitrexed and lead to increase toxicity are NSAIDs and beta-lactam antibiotics.
Drugs which reverses the action of Raltitrexed is Leucovorin (Folinic Acid) .
Drug which antagonizes the action of Raltitrexed is L-Asparaginase.
Drugs which are potentiated by Raltitrexed are 5-FU and Warfarin.

Toxicities: (1) Fatigue & malaise (Dose-limiting)
(2) Mucositis, nausea & vomiting,diarrhoea (May be dose-limiting)
(3) Bone marrow depression
(4) Transient elevation of liver transaminases

Routes of administration: IV only
Dose: 3 mg/m^2 IV every 3 weeks

Special points regarding administration:
Use with caution in patients with renal dysfunction

Indications:
(1) Advanced CRC
(2) NSCLC
(3) Ca. Breast

5-Fluorouracil

Chemical nature: Anti-metabolite
Fluoropyrimidine analogue

Cell-cycle specific (acts in S-phase)

Mechanism of action: 5-FU is activated to its active metabolite, FdUMP in the liver & cells, FdUMP is an inhibitor of the enzyme Thymidilate synthase (TS) [which converts dUMP to dTMP] . Inhibition of TS leads to accumulation of FdUMP, which then get incorporated into DNA and RNA in the form of dUTP, resulting in inhibition of DNA and RNA synthesis and function.

Mechanism of resistance: (1) Reduced affinity of TS for FdUMP
(2) Increased expression of TS
(3) Reduced incorporation of FdUMP into DNA or RNA

Pharmacokinetics: Oral absorption is variable (40-70%). After parenteral absorption it is widely distributed in the body including CNS and third space collections (pleural effusion/ascites). The highest concentrations are reached in the GI tract, BM and liver.
Metabolised in the liver and in cells to its active form

Excreted mainly via the kidney.
Interactions: 5-FU is potentiated by Leucovorin and by MTX and Trimetrexate. Leucovorin should be administered at least 30-60 minutes before 5-FU in order to increase the efficacy of 5-FU.
Toxic effect on DNA is ameliorated by Thymidine and on RNA by Uridine.

Toxicities: (1) Bone marrow depression (mainly with bolus 5-day regimes) (Dose-limiting)
(2) Mucositis, nausea & vomiting (mainly with infusional regimes)
(3) Skin rash (hand-foot syndrome)-mainly with infusional regime
(4) Cardiotoxicity (chest pain, ECG changes)
(5) Neurotoxicity (cerebellar)

Routes of administration: IV (bolus/infusion)
Dose: Bolus→ (monthly) 425-450 mg/m^2/day D1-D5 every 28 days
Infusion→ 800-1000 mg/m^2/day IV infusion (96 hr/120 hr) every 21-28 days

Special points regarding administration:
Contraindicated in patients with bone marrow dysfunction, active IHD or AMI within last 6 months or poor nutritional status.

Indications:

(1) CRC
(2) Ca. Breast
(3) Ca. H&N
(4) Ca. anal canal

(5) Ca stomach
(6) Ca.pancreas
(7) Ca.gall bladder
(8) Ca. oesophagus
(9) HCC
(10)BCC (topical)

Cytosine Arabinoside

Anti-metabolite
Cell-cycle specific (acts in S-phase)

Mechanism of action: Activated intracellularly into active metabolite Ara-CTP, which is incorporated into DNA resulting in chain termination and inhibition of DNA synthesis and function.
Mechanism of resistance: (1) Reduced activation of Ara-C
(2) Reduced cellular entry of Ara-C
(3) Increased breakdown of the drug.

Route of administration: IV or IT
Pharmacokinetics: Well absorbed after IV administration, distributed widely including CSF. Extensively metabolized. Excreted through urine.
Special considerations:
(1) When given IT, it must be diluted only in preservative-free normal saline.
(2) Should not be given in combination with L-Asparaginase, due to increased risk of acute pancreatitis.

Interactions: Potentiates action of alkylating agents, CDDP and RT.
Is potentiated by MTX & Fludarabine
Indications: (1) AML
(2) ALL
(3) CML
(4) NHL

Dose: Standard dose (induction phase of AML)=100 mg/m^2 /day by IVCI for 7 days
High dose (intensification phase of AML)= 1.5-3 gm/m^2 q 12 hourly for 3 days
Intra-thecal=10-30 mg up to 3-times weekly

Toxicities:
(1) Bone marrow depression (dose-limiting)
(2) Nausea & vomiting
(3) Neurotoxicity (cerebellar toxicity)-10% (especially if IT or high-dose systemic therapy)

(4) Ara-C syndrome in pediatric patients
(5) Conjunctivitis, keratitis
(6) Pulmonary toxicity
(7) Transient hepatic dysfunction
(8) Acute pancreatitis

Gemcitabine

Chemical nature: Anti-metabolite
Fluoropyrimidine analogue
Cell-cycle specific (acts in S-phase)

Mechanism of action: It is a prodrug which is activated by intracellular enzyme to active metabolite dFdCTP, which is incorporated into DNA and results in chain termination and inhibition of DNA synthesis and function.
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Mechanism of resistance: (1) Decreased activation
(2) Reduced metabolism
(3) Reduced cellular entry
Route of administration: IV

Pharmacokinetics: After short IV infusion,it is not well-distributed.Undergoes extensive metabolism and is excreted through kidneys.

Interactions: Potent radiosensitizer
Potentiates the action of CDDP.

Special considerations: Prolonged infusions >60 minutes are associated with increased toxicity.

Toxicities:
(1) Bone marrow depression (dose-limiting)
(2) Nausea & vomiting (70%)
(3) Diarrhoea (15-20%)
(4) Flu-like syndrome
(5) Transient hepatic dysfunction
(6) Infusion reaction
(7) Nephrotoxicity (proteinuria, hematuria and rarely HUS)
(8) Rash

Routes of administration: IV (3040 minutes IV infusion)

Dose: 1250 mg/m^2 IV Day 1 & 8, repeat cycle on Day 22
1000 mg/m^2 IV Days 1,8,15, repeat cycle on Day 28

Indications:

(1) NSCLC-1st line
(2) Ca. Pancreas-1st line
(3) Ca. Urinary Bladder-1st line
(4) Ca. Gall Bladder-1st line
(5) Ca. Breast-2nd line
(6) Ca. Ovary-2nd line

6-Thioguanine

Chemical nature: Anti-metabolite
Purine analogue
Cell-cycle specific (acts in S-phase)

Mechanism of action: It is a prodrug which is activated by enzymes including HGPRT. The active metabolite inhibits denovo purine biosynthesis. Incorporation of thiopurine triphosphate into DNA results in inhibition of DNA synthesis and function.
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Route of administration: PO

Pharmacokinetics: Absorption after oral administration is variable. Widely distributed. Metabolised in the liver to active metabolite. Metabolites are eliminated via both feces and urine.

Toxicities:

(1) Bone marrow depressinon
(2) Nausea & vomiting
(3) Mucositis and diarrhea
(4) Hepatic dysfunction
(5) Immunosuppression

Dose: 100 mg/m^2 BD PO D1-D5 q 4 weeks (combination)
1-3 mg/kg daily (single agent)

Indications:

(1) ALL
(2) AML
(3) CML

6-Mercaptopurine

Chemical nature: Anti-metabolite
Purine analogue
Cell-cycle specific (acts in S-phase)

Mechanism of action: It is a prodrug which is activated by enzymes including HGPRT. The active metabolite inhibits denovo purine biosynthesis. Incorporation of thiopurine triphosphate into DNA results in inhibition of DNA synthesis and function.
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Route of administration: PO

Pharmacokinetics: Absorption after oral administration is variable. Widely distributed. Metabolised in the liver to active metabolite. Metabolites are eliminated via urine.

Toxicities:

(6) Bone marrow depressinon
(7) Nausea & vomiting
(8) Mucositis and diarrhea
(9) Hepatic dysfunction
(10) Immunosuppression

Dose: 1.5-2.5 mg/kg/day

Indications: ALL

Capecitabine

Chemical nature: Anti-metabolite
Fluoropyrimidine analogue
Cell-cycle specific (acts in S-phase)

*Mechanism of action:*Capecitabine is a pro-drug of 5-FU. It is metabolized in the liver to 5'DFCR, which is then converted to 5-FU by the enzyme Thymidine Phosphorylase, which is present in greater concentration in tumor tissue as compared to normal tissue. 5-FU is activated to its active metabolite, FdUMP in the liver & cells, FdUMP is an inhibitor of the enzyme Thymidilate synthase (TS). Inhibition of TS leads to accumulation of FdUMP, which then get incorporated into DNA and RNA in the form of dUTP, resulting in inhibition of DNA and RNA synthesis and function.

Mechanism of resistance: (1) Reduced affinity of TS for FdUMP
(2) Increased expression of TS
(3) Reduced incorporation of FdUMP into DNA or RNA

Pharmacokinetics: Oral absorption is good. Food retards the absorption of the drug. It is activated by metabolism in the liver and in tumor cells. It is excreted mainly through urine (<90%).

Interactions: Capecitabine is potentiated by Leucovorin.
Capecitabine significantly potentiates the action of Warfarin, by retarding its metabolism and can result in serious bleeding episodes if it is used along with Warfarin.
Special considerations: Pyridoxine or Celecoxib can be given for prevention or treatment of hand-foot syndrome.

Toxicities: (1) Diarrhoea (dose-limiting)-occurs in 40% patients
(2) Hand-foot syndrome (palmo-plantar erythrodysaesthesia)-in 15-20% patients
(3) Bone marrow depression (less frequent than with 5-FU)
(4) Nausea & vomiting (20-40% patients)
(5) Elevation of Serum Bilirubin & Transaminases.
(6) Neurotoxicity (cerebellar)
(7) Cardiotoxicity (chest pain, ECG changes)

Routes of administration: PO
Dose: 1250 mg/m^2 BD PO D1-D14, 7 days gap, resume on Day 22

Indications:

(1) CRC (where infusional 5-FU administration will not be tolerated)
(2) Metastatic Breast Cancer (2^{nd} and 3^{rd} line, in anthracycline-resistant cases)

Fludarabine

Anti-metabolite
Cell-cycle specific(acts in S-phase)

Mechanism of action: Converted to its active metabolite F-ara-ATP, which is incorporated into DNA and results in inhibition of DNA synthesis and induction of apoptosis.

Indications: (1) CLL/SLL
(2) FL
Route of administration: IV/ Oral

Pharmacokinetics: After oral administration, absorption is variable. It is well absorbed after injection. Distributed widely. Metabolised in the liver. Excreted mainly by kidneys
Interactions: It potentiates the action of Ara-C, CDDP, Cyclophosphamide and Mitoxantrone.

Dose: 25 mg/m^2/day D1-D5 every 28 days

Toxicities:

(1) Myelosuppression (Dose limiting)
(2) Immunosuppression (increased risk of opportunistic infections such as PCP)
(3) Fever (due to release of cytokines)
(4) Nausea & vomiting
(5) Tumor lysis syndrome
(6) Hypersensitivity

Pentostatin

Anti-metabolite
Has both cell-cycle specific & non-specific effects
Mechanism of action: Inhibition of Adenosine deaminase→ accumulation of dATP ,which is toxic to the cells

Indications: (1) Hairy Cell Leukemia
(2) CLL/SLL
(3) CTCL
(4) ALL
Route of administration: IV
Pharmacokinetics: Excreted mainly unchanged by kidneys
Special considerations: It is absolutely contraindicated in combination with Fludarabine due to risk of fatal pulmonary fibrosis.

Dose: 4 mg/m^2 IV on alternate weeks
Toxicities:

(1) Myelosuppression (Dose limiting)
(2) Immunosuppression (increased risk of opportunistic infections such as PCP)
(3) Nausea & vomiting
(4) Hypersensitivity
(5) Headache, malaise

Cladribine

2-Chlorodeoxyadenosine
Anti-metabolite
Cell-cycle specific(acts in S-phase)

Mechanism of action: Inhibition of DNA synthesis, depletion of ATP and induction of apoptosis.

Indications: (1) Hairy Cell Leukemia
(2) CLL/SLL
Route of administration: IV/ Oral

Pharmacokinetics: After oral administration, absorption is variable. It is well absorbed after injection. Distributed widely. Metabolised in the liver. Excreted mainly by kidneys (50%)

Dose: 0.09 mg/kg/day by continuous infusion for 7 days for single course
Toxicities:

(7) Myelosuppression (Dose limiting)
(8) Immunosuppression (increased risk of opportunistic infections such as PCP)
(9) Fever (due to release of cytokines)
(10) Nausea & vomiting
(11) Tumor lysis syndrome
(12) Hypersensitivity
(13) Neurotoxicity