Chemotherapy Drugs

1. ALKYLATING AGENTS: Nitrogen Mustards

MOA: Interstrand crosslinks. Bifunctional electrophiles.
Prefer to react with Guanine

Mechlorethamine

Highly reactive
Toxic
Used in MOPP regime (Hodgkins)

Melphalan

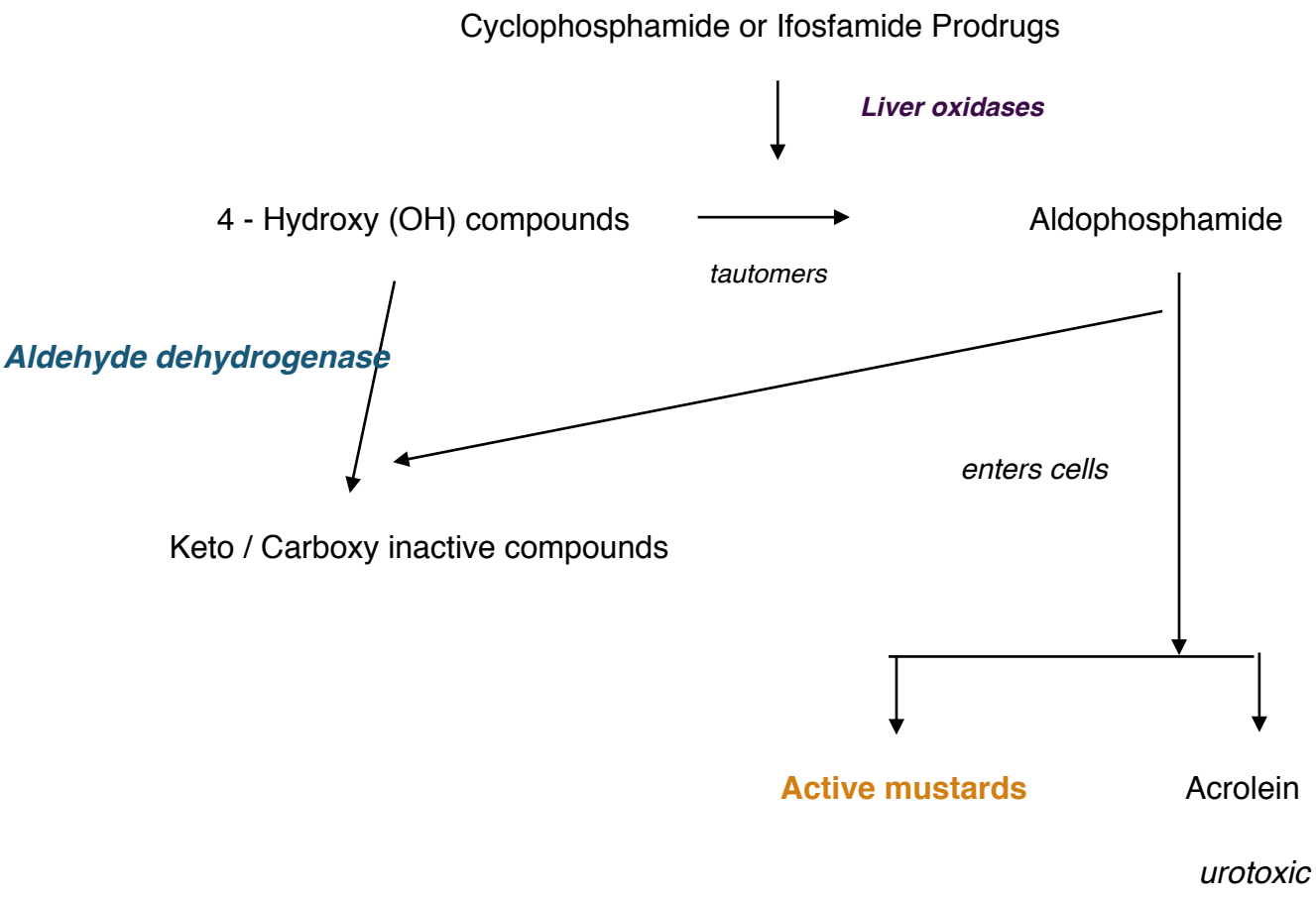
Oral or IV
Variable bioavailability

Uptake by active transport carrier protein.
↓ uptake = resistance

Elimination: Spontaneous hydrolysis.
Some role of kidneys too

Used in Bone marrow transplant regimes

CYCLOPHOSPHAMIDE AND IFOSFAMIDE



Cyclophosphamide

Prodrug

liver oxidases

Cyclophosphamide — > phosphoramide mustard (active)

Oral (>75% bioavailability) or IV

Elimination: **CYP2B6.** Hepatic metabolism to inactive compounds. Renal excretion.

Cyclophosphamide is an enzyme inducer and induces its own metabolism. Metabolism of cyclophosphamide is much quicker than ifosfamide. Half life 2-8 hrs (half life of ifosfamide is 6-15 hrs)

Dose limiting toxicity: Myelosupression

Relative sparing of platelets and stem cells due to increased aldehyde dehydrogenase (inactivates drug intracellularly)

Characteristic S/E:

- nausea, vomiting, hair loss, gonadal damage.
- >1500mg/m2 highly emetogenic
- SIADH like syndrome (drug has an ADH like effect)
- Radiation Recall

Very high doses 60mg/kg can causes irreversible myocardial necrosis

Acrolein is a metabolic byproduct - causes haemorrhagic cystitis.

Ifosfamide

Prodrug

liver oxidases

Ifosfamide — > ifosfamide mustard (active)

IV

Elimination: **CYP3A4**. Hepatic metabolism to inactive compounds. Renal excretion.

Metabolism similar to cyclophosphamide but decreased liver oxidases action due to low affinity and ↑ dechloroethylation.

Therefore higher doses of ifosfamide can be used and different toxicity profile.

Characteristic S/E:

- Increased neurotoxicity due to more chloro-ethyl acetaldehyde derivatives. Treatment is with methylene blue

Onset 12 hrs - 6 days post dose
Symptoms: confusion/somnolence/ seizures/coma
Risk factors for neurotoxicity:
↓ ALBUMIN
↑ Creatinine
Pelvic disease

- ADH like effect
- Fanconi syndrome (renal tubular damage)

Acrolein production is MORE common- causes haemorrhagic cystitis.
Treated with Mesna.
Mesna is inactive in plasma and only activated in urine.
2nd line treatment - Aluminum-potassium-sulphate
3rd line Rx - Carboprost

Dose modification: Renal and hepatic disease

Mechanisms of resistance: Increased Aldehyde dehydrogenase (increased deactivation)
Increased glutathione (more DNA repair)
Increased DNA repair via MGMT (which inhibits apoptosis due to damaged DNA)

1 b. Alkylating agents: Nitrosureas

Eg. Carmustine, Lomustine, Streptozocin

Carmustine and Lomustine
Lipid soluble
Can reach CNS
Limited clinical use - toxic to normal tissues and highly leukemogenic

Carmustine (BCNU)	Lomustine (CCNU)
IV ONLY	ORAL
	Used in brain tumours
Rapid metabolism: no compounds in plasma or urine seen	

STREPTOZOCIN = Only *methyl*nitrosurea
Used in pancreatic islet cell tumours
Minimal myelotoxicity
Diabetogenic

1 c. Alkylating Agents : Alkyl Sulfonate

Eg. Busulfan

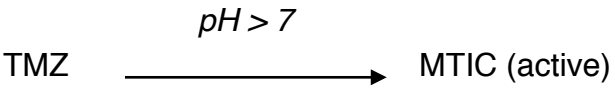
Selective action on blood cells. Used in CML + Bone marrow transplant.
Hepatic metabolism

Side effects: Can include Veno occlusive disease, marrow aplasia and pulmonary fibrosis

1 d. Alkylating Agents: Triazenes

Temozolamide (TMZ):

Oral drug:
99% oral absorption. Stable in acidic pH in stomach.
Labile if pH > 7 (i.e. in normal blood pH)



TMZ crosses blood brain barrier and 40% concentration achieved in CSF
Environment around gliomas is more basic and therefore preferential activation.

MOA:
Monoalkylating at O6
DOES NOT require CYP metabolism (Dacarbazine : Requires CYP metabolism)

O6 methylation is removed by MGMT enzyme. MGMT is a suicide enzyme and therefore more needed to continue to repair O6 methylation.
HYPERMETHYLATED MGMT Gene is silenced. Therefore less repair and more TMZ efficacy

Characteristic Side effects:
Predominantly lymphopenia (?consider PCP prophylaxis)
Hepatic toxicity
Photosensitive rash

1 e. Alkylating agents: METAL SALTS

Examples: Cisplatin and Carboplatin

MOA:
Platinum molecule with 2 Chloride side groups in cisplatin are 'aquated' in cells or replaced with water molecules. This results in binding of the cisplatin molecule to DNA, preferentially INTRA Strand cross links across adjacent N7 of guanine. This distorts the DNA strand.

Can cause inter strand cross links as well to a lesser extent.

Oxaliplatin consists of platinum molecule with oxalate and 2 DACH (diaminochloride groups)

Uptake into cells:
Active transport via OCT (Organic cation transporter)

Resistance to Cisplatin:
1. Low OCT levels (low uptake)
2. High capacity for Nucleotide excision repair (the intra strand cross links caused by cisplatin are repaired by NER)
3. Basic environment. Cisplatin in less active in bases and more active in acidic environment
4. ERCC1 over expression (high capacity for DNA repair)

Characteristic Side Effects:

1. Nephrotoxicity. Direct damage to tubules. (Cisplatin > Carboplatin>Oxaliplatin)
2. Salt wasting especially seen with cisplatin (Mg, K, wasting through renal tubules)
3. High uric acid levels
4. Neurotoxicity. Cisplatin > Oxaliplatin > Carbolpaltin. Cisplatin - damage to large sensory nerves. Oxalplatin - small nerves preferentially damaged due to DACH groups or diaminochloride groups in ring structure.

5. Hypersensitivity reactions after Cycle 6 (IgE type reactions with foreign body recognition in initial exposures and memory cell formation followed by trigger of Type 1 Hypersensitivity reaction in later cycles)
6. Ototoxicity seen with Cisplatin (4000-8000Hz or high frequency)
7. Carboplatin causes thrombocytopenia > neutropenia > anaemia. Dose limiting toxicity is thrombocytopenia.
8. Oxaliplatin - causes peripheral sensory neuropathy. Pharyngolaryngeal dysesthesia, especially reaction to cold are typical hypersensitivity reactions to oxaliplatin.
9. Oxaliplatin side effect includes PRES (8 days to 6 weeks post treatment)

Dose modification in ONLY Renal disease

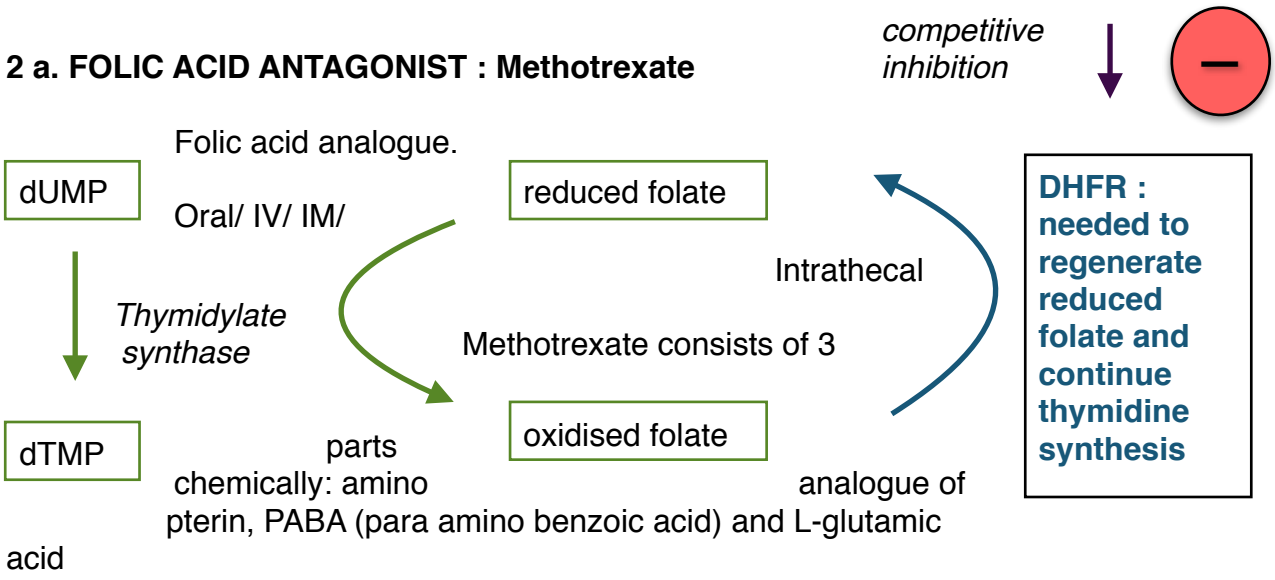
2. ANTIMETABOLITES

Do not directly interact with DNA with decrease production of nucleotides and thus prevent normal DNA replication. Less problems with drug induced carcinogenesis as does not directly damage DNA (unlike alkylating agents).

Duration of exposure is more important than peak concentration of drug or AUC. (Drug must be present during S phase of tumour cell to have effect, duration of exposure above minimum threshold concentrations is key)

METHOTREXATE

2 a. FOLIC ACID ANTAGONIST : Methotrexate



MOA:

1. Inhibits denovo purine biosynthesis
2. Inhibits Dihydrofolate reductase (DHFR) needed for thymidine synthesis

dUMP = deoxyuridine monophosphate. dTMP = deoxythymidine monophosphate

Methotrexate Uptake into cells:
Active transport (reduced folate carrier)
At higher concentrations - some passive diffusion

Methotrexate forms **polyglutamates** in cancer cells. (more in cancer cells than normal cells). Intracellular polyglutamates competitively inhibit DHFR. Polyglutamates are harder for tumour cells to efflux out of cells. They also engulf DHFR and limit rescue by folinic acid in cancer cells.

Reversal of toxicity:

1. Folinic Acid/ FH4 / 5 - formyl tetrahydrofolate. Used in high dose MTX therapy for normal cell rescue. Required if dose is > 500mg/m2
2. Glucarpidase: Used to treat severe MTX toxicity. Recombinant bacterial enzyme. Very expensive. Breaks down methotrexate (MTX).

Advantages of high dose MTX therapy:
More Uptake by tumour cells
CNS penetration

MTX can sequester in third space fluid (ascites, pleural effusion) and cause life threatening toxicity after high dose methotrexate.

Metabolised to 7 - OH methotrexate in liver. Excreted by kidneys.

Excretion limited by weak acids such as penicillin, aspirin, probenicid, ciprofloxacin.
Aspirin and trimethoprim displace MTX from albumin binding

Both ↑ TOXICITY

Characteristic Side effects:

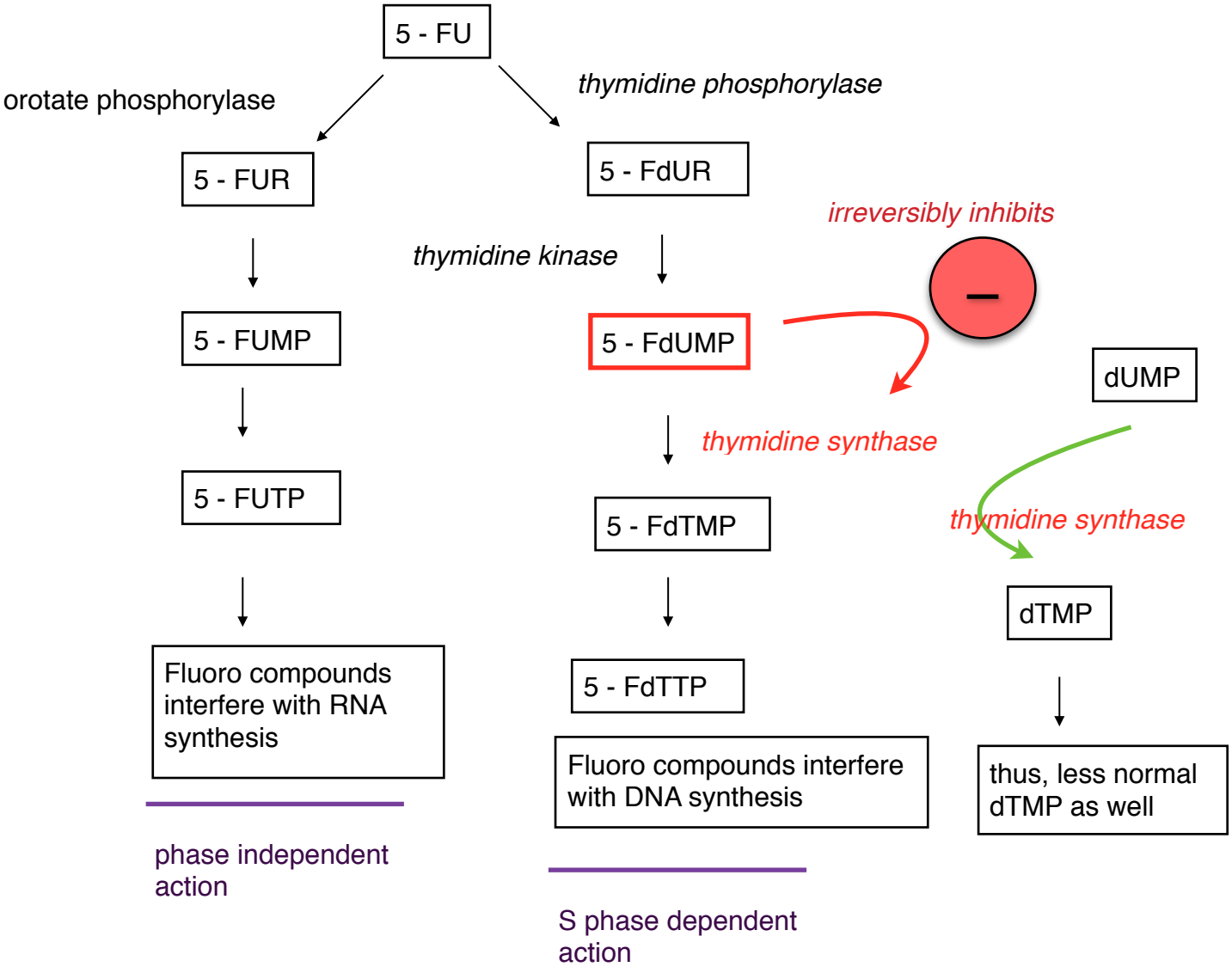
Myelosupression - usually within 5-7 days (Early compared to other chemotherapy drugs!)
Mucositis/GI toxicity
Renal damage - crystal precipitation in tubules. Need increased output of alkaline urine to avoid. UO >100ml/hour and pH >7. Avoid NSAIDS.

Dose modification required in hepatic and renal disease.

2 b. Pyrimidine Analogues

5 - FU

Resembles Uracil and Thymine
IV Only : Given as bolus or infusion



(5-FdUR = 5 deoxy 5'fluorouridine, 5- FdUMP = 5 deoxy, 5'fluorouridinemonophosphate, 5-FdTMP = 5 deoxy, 5 fluorothymsidine monophosphate.)

Non linear pharmacokinetics or saturable metabolism
Catabolism end products : (Metabolised in the liver) = CO2 + urea + beta alanine

Rate limiting enzyme for catabolism = DPD (Dihydropyrimidine dehydrogenase)
DPD deficiency leads to life threatening toxicity.

Folinic Acid and 5FU
Thymidylate synthase + 5 FU + Folinic Acid forms a ternary complex. And excess folinic acid means that the complex is more stable. Therefore more inhibition of Thymidylate synthase for longer. More chemotherapeutic action and more toxicity.

Characteristic toxicity:

	Bolus Dose	**Infusion**	**Bolus + folinic acid**
Dose limiting toxicity	Bone marrow suppression	Mucositis	Diarrhoea

Other toxicity = rash, PPE, ataxia (cerebellar toxicity), coronary spasms and cardiotoxicity.

Dose modification required in reduced hepatic function.

PEMETREXED

Multiple MOAs

1. Inhibits Thymidine synthase (MAIN MECHANISM)
2. Inhibits Dihyrofolate reductase
3. Inhibits GARFT (Glycinamide ribonucleotide formyl transferase)

Polyglutamate forms in cells are increasingly efficacious.

Folic Acid and B12 is prescribed with Pemetrexed to decrease haematological and GI toxicity.
High levels of homocysteine at baseline are a marker of endogenous B12 deficiency and also predict Pemetrexed toxicity.

Avoid NSAIDS and nephrotoxins with pemetrexed
Dose reduction required in Renal disease.

<u>Ralitrexed -</u> direct thymidine synthase inhibitor

TRIFLURIDINE TIPIRACIL (LONSURF)

MOA:
Small molecule TP **(thymidine phosphorylase)** inhibitor

ORAL drug
Poor protein binding
excreted unchanged - no real metabolism

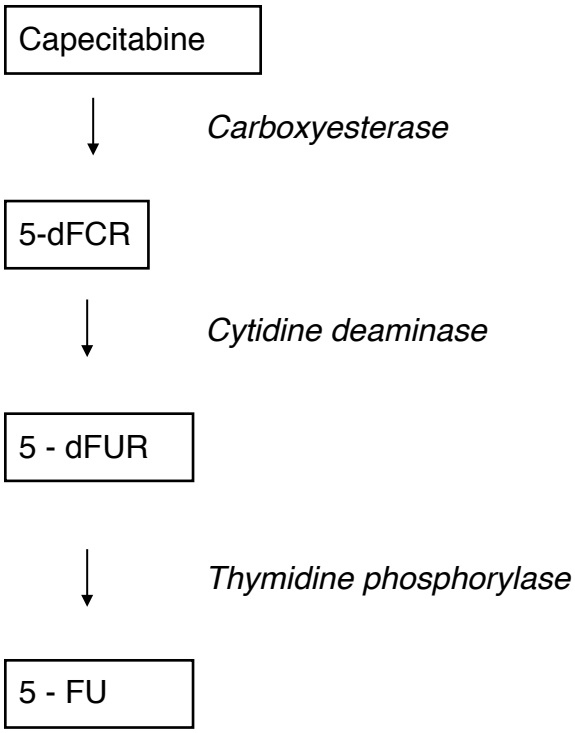
Main function of tipiracil is to increase trifluridine bioavailability

Used in: Metastatic Colorectal cancer

TP also also associated with PDGF and angiogenesis (an activation of 5FU) and thus it's inhibition has independent anticancer activity too.

<u>CAPECITABINE</u>

ORAL prodrug of 5-FU
(5dFCR = 5 deoxy, 5'flurocytidine)



Characteristic Side Effects:

PPE worse with Capecitabine as ↑ thymidine phosphorylase in hands. Treat with emollients.

Acute cerebellar syndrome onset can be weeks to months after dose. Usually reversible

5FU causes more cardiac and cerebellar toxicity Capecitabine causes more PPE and diarrhoea.

Increased toxicity with gemcitabine, metronidazole and thiazides.

Dose modification required in reduced hepatic and renal function.

ARA-C or CYTARABINE

Pyrimidine analogue and antimetabolite
Activated by deoxycytidine kinase to Ara-Cytosine-Triphosphate

Dose limiting toxicity: Leukopenia and thrombocytopenia. Megaloblastosis common.

Uncommon toxicities: Neurotoxicity (cerebellar), hepatotoxicity with cholestatic jaundice and pulmonary syndrome (1-2 weeks post treatment)

Used in acute myeloid leukemias.

GEMCITABINE (dFdC - deoxy fluro deoxy cytidine)

Pyrimidine analogue and antimetabolite. Similar to Ara-C but more active in solid tumours. Half life of intracellular dFdCTP much longer than Ara-C metabolites. Therefore weekly dosing of gemcitabine is possible.

dFdC is activated to triphosphate form by cytidine kinase.

MOA:
It is a DIRTY DRUG

1. Inhibits DNA synthesis (antimetabolite). Causes masked chain termination. After addition of dFdCTP, only more more nucleotide can be added and then the chain stops. This last nucleotide masks the dFdCTP and prevents DNA repair.
2. Inhibits deoxynucleotide metabolism that is responsible for forming deoxy compounds from ribonucelotides. (Inhibits Ribonucleotide reductase RNR)

RNR

Ribonucleotides ——————> deoxyribonucleotides

3. Induces apoptosis via p38 MAPK pathway.
4. Inhibits self metabolism (by inhibiting deoxy cytidine deaminase required by breakdown of dFdCTP)

Uptake into cells by active transport - hENT (human equilibriance nucleoside transporter)

Mechanism of Resistance:

1. ↓ uptake by hENT1
2. ↑ RNR subunits. Therefor enzyme is able to produce more native deoxyribonucleotides

Characteristic Side Effects:

Flu like syndrome (infusion reaction)
HUS - Hemolytic uraemia syndrome
Thrombotic microangiopathy
Peripheral edema
Pulmonary syndrome: **DO NOT GIVE Gemcitabine with Thoracic Radiotherapy. Can cause severe pulmonary toxicity.**
Transaminitis

No specific dose modification advice in renal or hepatic disease

3. NATURAL PRODUCTS

3a. Anthracyclines
3b. DNA Binding - Bleomycin, Mitomycin C
3c. TOPOISOMERASE I inhibitors
3d. TOPOISOMERASE II inhibitors
3e. Microtubule polymerisation

3a. ANTHRACYCLINES

Daunorubicin - first product. From steptomyces in soil.

Doxorubicin
Idarubicin (ORAL)
Epirubicin - 3D structure different, 4' epimer of doxorubicin with different orientation of hydroxyl group on Carbon 4. The effect is a compound that is less toxic and eliminated faster though glucuronidation.

MOA:

1. DNA intercalation
2. Topoisomerase II inhibition
3. Free radical generation (quinone ring —-> semiquinone radical and free Oxygen radicals. Thought to be a major mechanism of cardiotoxicity)
4. Cell membrane effects - binds to charged lipids like cardiolipin and lyses cells without entering them.

Lipid soluble, Large Vd. Terminal half life 48 hours.
Vesicants
Hepatic Metabolism and Biliary Excretion

RED product. The chemotherapy bag looks red. Red urine for 48 hours after treatment.

Characteristic Side effects

Tissue necrosis if extravasates (vesicant)
Cardiotoxicity: Acute < 2 weeks, Early chronic < 1 year, Late chronic > 1 year post dose
Cumulative maximum dose 450mg/m2
Oxygen radical damage sarcoplasmic reticulum.
Dexrazoxane is an iron chelator and is licensed for use at >300mg/m2 of doxorubicin dose to prevent cardiotoxicity.

Mechanisms of Resistance:

Increased Efflux though Pgp or MDRP (efflux pumps)
Increased glutathione (scavenges free oxygen radicals)

Dose reduction required in hepatic disease

Epirubicin - maximum cumulative dose licensed is 900mg/m2. Dexrazoxane can be used as a preventive agent at doses > 540mg/m2.

3b. BLEOMYCIN

Isolated from fungal cultures
Inhibits cells in G2 phase

MOA:
Bleomycin ferrous complexes (intracellular) —> binds to DNA —> insertion of drug between base pairs and DNA unwinding —> free radical formation and damage to DNA.

Ratio of SSBs to DSBs about 10:1
Also causes oxidative degradation of RNA

Metabolism: Bleomycin hydrolase. Inactivates bleomycin in cells. (Lack of bleomycin hydrolase in lungs predisposes to pulmonary toxicity.)
Excreted in Urine.

Cumulative maximum life time dose = 400 units

Characteristic Side Effects:

1. Little bone marrow effect
2. Rash/fever/chills/mucositis

3. Lung FIBROSIS/ Pulmonary Toxicity - Insidious onset. 1-3% risk of death in those affected.
Risk factors include age >70 yrs, poor renal function (<35ml/min GFR), cumulative dose, high supplemental oxygen exposure, prior chest Radiotherapy, exposure to filgastrim (GCSF).

Glutathione can also INCREASE damage due to Bleomycin.

3b MITOMYCIN C

Derived from Streptomycin fungi.
Blue coloured Chemotherapy drug.
Vesicant
Hepatic metabolism and Renal Excretion.

MOA: Causes damage by direct DNA binding (acts like an alkylating agent)
Preferential toxicity to hypoxic cells. Therefore useful for hypoxic tumour cell killing.

Characteristic Side Effects

1. Dose limiting toxicity is Leukopenia and thrombocytopenia. Delayed myelosupression - can take 8 weeks or 2 months!
2. Haemolytic Uraemic Syndrome
3. Interstitial Lung Disease and pulmonary fibrosis.
4. BRONCHOSPASM if given with vinca alkaloids
5. Veno occlusive disease (rare)

Dose reduction in renal and hepatic disease.

3c. 3d. TOPOISOMERASE Inhibitors

	TOP II Inhibitors	TOP I Inhibitors
Natural origin	Mandrake Plant	Chinese tree (Camptotheca derivatives)
Examples	Etoposide, Teniposide	Irinotecan, Topetecan
MOA: Enzyme inhibited	Topoisomerase II - TOP II causes DSB in DNA to help unwind strands and then re-ligates them. Also important in chromatid separation. TOP II inhibitors prevent re-ligation and result in multiple DSBs	Topoisomerase I - TOP I causes SSBs in DNA to help with unwinding strands. Also plays a role in re-ligating the breaks. TOP I inhibitors inhibit these processes . Due to lack of relaxation of coils and SSBs, further damage occurs when replication fork reaches site and results in DSB.
Cell cycle phase active in	G2 phase	S phase
Route of administration	Etoposide - Oral or IV. Teniposide IV	Both IV
	Etoposide highly protein bound. Careful dose adjustments with low albumin levels.	
Prodrug metabolised to		SN 38 (Irinotecan acted on by carboxyesterase enzymes to form SN38)
Metabolism/Detoxification	Hepatic glucuronidation	Hepatic glucuronidation

	TOP II Inhibitors	TOP I Inhibitors
Dose limiting toxicity	myelosupression and hair loss. Note: Etoposide is leukemogenic	Topetecan - myelosupression Irinotecan - diarrhoea and myelosupression. Note: Glucuronated SN38 is excreted through the biliary system. In the gut, bacteria can reactivate SN38 by deglucuronidation. This results in direct mucosal damage due to SN38 and diarrhoea. Note: Less risk of secondary cancer with TOP I inhibitors as do not directly damage DNA or directly cause DSBs.
Mechanisms of resistance		Irinotecan - decreased carboxyesterase levels, therefore decreased activation to SN38
Dose modification	Etoposide - renal and hepatic disease	Topetecan - renal and hepatic disease Irinotecan - hepatic disease only.

3e. Drugs acting on MICROTUBULES : Taxanes and Vinca-alkaloids.

TAXANES

Docetaxel, Paclitaxel, Cabazitaxel

Derived from Western Yew Tree.

MOA: Inhibit micro tubular disassembly (stabilise microtubules and interfere with normal function). Bind to negative end of tubulin. Hence prevents mitotic spindle function. Active in M phase of cell cycle.

Significant tissue binding and large Vd. Terminal half life 10-12 hours.

Hepatic metabolism and biliary excretion. CYP3A4 and CYP 2C8

Characteristic Side effects:

1. Non cumulative myleosupression (neutropenia)
2. Peripheral neuropathy
3. Bradycardia and hypotension with infusion
4. Paclitaxel: Hypersensitivity reaction to 1st dose of infusion, often within minutes. Attributed to cremaphor solvent.
5. Docetaxel - causes fluid retention and skin and nail changes.
6. Nab paclitaxel (nano particle albumin bound paclitaxel) - less reactions and less neurotoxicity.

Mechanism of resistance: Increased beta tubulin monomers. Increased MDR1 protein or P glycoprotein (efflux pumps)

Order of Chemotherapy: Taxanes first ——> then Carboplatin. This order decreases the risk of thrombocytopenia although the mechanism is not entirely clear.

Efficacy of taxanes:

Paclitaxel	⟶	Docetaxel	⟶	Cabazitaxel
	if resistant	(2 x more potent)	*if resistant*	(less affinity for Pgp)

Eg. In metastatic prostate cancer: docetaxel used as first line chemo followed by cabazitaxel as second line.

Dose adjustment in hepatic disease.

VINCA ALKALOIDS

Examples: Vincristine, Vinblastine, Vinorelbine

Derived from Periwinkle plant (Madagascar)
Vesicants (treat with a warm compress unlike other extravasation reactions)

MOA: Bind to beta tubulin (positive end). Inhibit polymerisation to form microtubules and hence prevents mitotic spindle formation.

Signifiant tissue binding, large Vd. Terminal half life 40 hours

Hepatic metabolism and biliary excretion.

Characteristic toxicity:

1. Common side effects for all Vincas: peripheral neuropathy, myelosupression, increased ALT/AST (hepatoxicity), SIADH, constipation (autonomic neuropathy)
2. Peripheral neuropathy is due to side effects on axonal tubulin.
   Vincristine > Vinorelbine > Vinblastine
3. Life threatening bronchospasm if given with Mitomycin C

	Vinblastine	Vincristine	Vinorelbine
Dose limiting side effect	Myelosupression	Peripheral neuropathy	Myelosupression

Mechanism of resistance: Increased beta tubulin monomers. Increased MDR1 protein or P glycoprotein (efflux pumps)

Dose adjustment in hepatic disease.

ERIBULIN

Microtubule dynamics inhibitor. Binds to positive end of soluble tubulin and prevents formation of mitotic spindles.

Side effects: Myelosupression, neuropathy, QTc prolongation

References:

1. The basic science of oncology editors, Ian F. Tannock, Richard P. Hill.- 3rd ed. **THE CHAPTERS ON PHARMACOLOGY IN Tannock and Hill are excellent.**
2. Washington Manual of Oncology, 3rd Edition 2015. Authors/Editor: Govindan, Ramaswamy; Morgensztern, Daniel. Publisher: Lippincott Williams & Wilkins
3. Notes by Dr. Oliver Coen, SpR Leeds Cancer Centre. Personal communication.