Alkylating agents

Mechanism of action: DNA cross-linking (intra- & inter-strand)→inhibition of DNA synthesis→apoptosis.
All are cell-cycle non-specific.
Pharmacokinetics: Widely distributed. Metabolised in the liver to active metabolites. Excreted through urine.
Members:

- Classical→ Nitrogen mustard, Cyclophosphamide, Ifosfamide, Chromabucil, Busulfan, Melphalan, Thiotepa
- Non-classic→ Dacarbazine, Temozolamide
- Nitrosoureas→ BCNU (Carmustine), CCNU (Lomustine), Streptozocin
- Anti-tumor antibiotics→ Anthracyclines eg Doxorubicin, Daunorubicin, Idarubicin, Epirubicin
  Actinomycin-D
  Bleomycin
  Mitomycin-C
  Mitoxantrone
- Platinums→ Cisplatin, Carboplatin, Oxaliplatin
- Others→ Procarbazine,

Anthracyclines

Doxorubicin
Epirubicin
Daunorubicin
Idarubicin

Chemical Nature Anti-tumor antibiotics, Alkylating Agents,
Specificity Cell-cycle non-specific.
Mechanism of action:

(1) Generation of free-radicals→DNA strand-breaks
(2) Intercalate within DNA→ inhibition of DNA synthesis & function
(3) Inhibit Topoisomerase II enzyme→ DNA breaks
(4) Inhibit DNA-dependant RNA polymerase→ inhibits transcription

Pharmacokinetics: All are poorly absorbed orally but well absorbed after IV administration. Widely distributed. Metabolised in liver to active metabolites (eg doxorubicinol). Excreted through feces.

Toxicities:

(1) Bone marrow suppression (dose-limiting)
(2) Nausea & vomiting (severe)
(3) Diarrhoea
(4) Alopecia
(5) Cardiotoxicity (acute=myopericarditis & conduction abnormalities, chronic= dilated cardiomyopathy)
(6) Reddish discolouration of urine

(7) Discolouration of nail, hyperpigmentation of skin
(8) Radiation-recall dermatitis
(9) Strong vesicant

Indications:
Doxorubicin→ Ca Breast, ALL, NHL, HD, Soft Tissue & Bone Sarcomas, HCC, Ca Stomach, SCLC,
Idarubicin→ AML, ALL
Daunorubicin→AML, ALL
Epirubicin→ Ca Breast, Ca Stomach

Doses:
Doxorubicin=40-60 mg/m^2 IV every 3 weeks
Daunorubicin=45 mg/m^2/day IV D1-D3
Idarubicin=12 mg/m^2/ day IV D1-D3
Epirubicin= 100-120 mg/m^2 IV every 3-weeks

Life time doses:
Doxorubicin=450 mg/m^2
Idarubicin=150 mg/m^2
Daunorubicin=550 mg/m^2
Epirubicin=900 mg/m^2

Topoisomerase I inhibitors/Camptothecins

Irinotecan
Topotecan

Specificit:y Cell-cycle non-specific
Mechanism of action: Inhibit the enzyme Topoisomerase I→ DNA double-strand breaks→ apoptosis.

Pharmacokinetics: Well-absorbed after parenteral administration. Widely distributed. Metabolised in the liver. Excreted through feces (irinotecan),urine (topotecan).

Indications:
Irinotecan→ Metastatic CRC 1st & 2nd line
Topotecan→ Ca ovary (2nd line)
SCLC (2nd line)

Dose:
Irinotecan=125 mg/m^2 IV weekly
Topotecan=1/5 mg/m^2/day IV D1-D5 every 3-weeks

Toxicities:

(1) Bone marrow depression (dose-limiting)
(2) Diarrhoea-early (cholinergic) & late (due to GI irritation)-only with Irinotecan
(3) Asthenia & fever
(4) Alopecia
(5) Hematuria (microscopic)-only with Topotecan

Topoisomerase II inhibitors/Epipodophyllotoxins

Etoposide
Teniposide

Specificity: Cell cycle specific (S-G2 phase)
Mechanism of action: Inhibit the Topoisomerase II enzyme, leading to prevention of DNA unwinding→ ultimately to inhibition of DNA synthesis.
Pharmacokinetics:
Oral absorption of Etoposide is good but unpredicatable at higher doses, oral dose is double the dose given IV.
Teniposide is only administered via IV route.
Widely distributed.
Metabolised in the liver. Excreted via the kidney.

Indications:
Etoposide→ SCLC, NSCLC, Germ Cell Tumors,
Teniposide→ ALL
Doses:
Etoposide= 100-120 mg/m^2/ day IV D1-D3 every 3 weeks (EP-SCLC/NSCLC)
100 mg/m^2/ day IV D1-D5 every 3 weeks (BEP-GCT)
Teniposide=165 mg/m^2 IV twice weekly every 4 weeks

Toxicities:

(1) Bone marrow depression (dose-limiting)
(2) Hypersensitivity
(3) Nausea & vomiting
(4) Alopecia
(5) Diarrhoea
(6) Thrombophlebitis
(7) Radiation-recall dermatitis (Etoposide)
(8) Second malignancies (AML)

Lipodox

Special points:

(1) Liposomal encapsulated form of Doxorubicin. It is protected from enzymatic digesion. Decreased plasm protein binding. Decreased uptake in normal tissues. Preferentially taken up by tumor tissues where Doxorubicin is released.

(2) Dose=50 mg/m^2 IV every 4 weeks
(3) Indications=Ca ovary (2^{nd} line) & AIDS-related KS (refractory)
(4) Administration=as an IV infusion over 30 minutes diluted in 250 ml 5%D

Dexrazoxane

It is a chemoprotective drug. It is hydrolysed in vivo to an EDTA-analog, which chelates iron away from Doxorubicin-iron complexes→ prevent free radical generation→ reduces cell damage.
Given IV 30 minutes before Doxorubicin. Dose= 10-times the dose of Doxorubicin.
Indicated for prevention of anthracycline-mediated cardiotoxicity in patients of MBC who have already received at least 300 mg/m^2 of Doxorubicin.