به نام یزدان پاک

ALKYLATING AGENT

The first anticancer:

Alkyl Sulfonates:	Busulfan	
Aziridines:	Thiotepa	
Triazines:	Temozolomide	dacarbazine
Nitrosoureas:	Streptozotocin	carmustine
Nitrogen Mustards:	Melphalan	chlorambucil
	Cyclophophamide	ifosfamide

Alkyl Sulfonates

Busulfan

- Use in CML (myeloid cells > lymphoid cells)

Dose& administration

Parentral

Oral (Bioavailability: 80%):

4-8mg(1.8mg/m2)daily Po

640mg/m2 for bone marrow transplant daily Po

Toxicity

- Bone marrow: treatment can lead to prolonged hypoplasia.
- Skin: Hyperpigmentation
- Platelet: count - activity ⇩
- Veno occlusive dis (in high dose)
- Neurotoxicity &seizures: (in high dose) phenytoin for **treatment** and clonazepam and lorazepam for **prevention**.
- Pulmonary fibrosis fatal: If busulfan is stopped before the onset of clinical symptoms, pulmonary function may stabilize

Triazenes

Temozolomide

- Oral: Rapidly absorbed
- Acts as a prodrug of dacarbazine
- Food reduces the rate and extent of drug absorption.
- Crosses the blood brain barrier (concentrations 30%).

Use in: melanoma, glioma, astrocytoma, brain metastasis, refractory leukemia

Dose: 150 mg/m2 PO daily for 5 days every 28 days.

Toxicity

Nausea, vomiting, myelosuppresion, Mild elevation in hepatic transaminases, Headache, fatigue, Photosensitivity.

Dacarbazine(DTIC)

Use in melanoma, sarcoma and HL. Administration: IM ; IV

Toxicity

- **Nausea , vomiting**
- Myelosuppresion
- Flu-like syndrome
- CNS toxicity: paresthesias, neuropathies, ataxia, lethargy, headache, confusion, seizures.
- Pain and/or burning at the site of injection.

Nitrogen Mustards

Cyclophosphamide (Cytoxan)

To treat a variety of immune-related diseases and to purge bone marrow in autologous marrow transplant

Administration: IV PO

Activated in the liver phosphoramide mustard and **acrolein**

Phenobarbital, phenytoin→ stimulate P450 sys → ↑metabolic activation of cyctoxan to its cytotoxic metabolites.

Toxicity

Myelosuppression is dose-limiting: leukopenia

Immunosuppression

(1) suppression of B-lymphocyte function
(2) depletion of B-lymphocytes
(3) suppression of T-lymphocytes

SIADH

Alopecia may be quite severe, especially in combination with vincristine or doxorubicin. regrowth of hair occurs after cessation of therapy with a change in the color and greater curl.

Nausea and vomiting occurs within 2–4 hours of therapy, and may last up to 24 hours

Bladder toxicity in the form of hemorrhagic cystitis, begin within 24 hours or may be delayed for up to several weeks. mesna and hydration must be used with high-dose therapy.

Drug Interaction

- decreases the plasma levels of digoxin
- effect of anticoagulants 
- Cyclophosphamide may increase the risk of doxorubicin- induced cardiotoxicity.

ifosfamide

Activated by the liver cytochrome P450 microsomal system

Administration: IV

Dose: 1.2 g/m2/day IV for 5 consecutive days

Toxicity

Cardiac toxicity:

Dose related CHF: transient & reversible
At dose >16g/m2
Subacute: mean 12days

Hemorrhagy: range from a mild cystitis to severe bladder massive hemorrhage

Preventation: MESNA is given in divided doses every 4 hours in dosages of 60% of those of the alkylating agent

Treatment:
- hydration
- continuous irrigation with a solution containing (MESNA)
- frequent bladder emptying

Drug Interaction

Phenobarbital / phenytoin : stimulate the liver P450 and activation of ifosfamide

effect of anticoagulants ⬆

Cisplatin: ifosfamide-associated renal toxicity ⬆

Anti Topoisomerase

DNA topoisomerases are a general class of enzymes that alter the topology of DNA

Camptothecin is alkaloid that identified in the 1960s in a screen of plant extracts for antineoplastic drugs.

Irinotecan

Irinotecan is FDA approved for the treatment of colorectal cancer but is also active in the treatment of small-cell and non-small-cell lung cancers, gastric cancer and cervical cancer

Irinotecan is a prodrug that cleaves and eliminates by liver

Administration & Dose

Irinotecan is usually administered intravenously

- weekly infusion of 125 mg/m2- for 4 weeks with a 2-week rest period
- alternatively, 240 to 350 mg/m2 every 3 weeks

toxicities

The most common toxicities associated with irinotecan are diarrhea and myelosuppression.

Two mechanisms are involved in irinotecan-induced diarrhea:

1) Acute cholinergic effects produced by inhibition of acetylcholinesterase by the prodrug can cause abdominal cramping and diarrhea in less than 24 hours ,which can be treated with administration of atropine.

2) Mucosal cytotoxicity that leads to diarrhea after 24 hours can be treated with loperamide

Topotecan

it is approved for the treatment of ovarian cancer, small-cell lung cancer and cervical cancer.

Administration & Dose

it is administered intravenously at a dose of **1.5** mg/m2 as a 30-minute infusion daily for 5 days, followed by a 2-week period of rest

it is administered Orally at a dose of **2.3** mg/m2 daily for 5 days, followed by a 2-week rest

toxicity

The most common dose-limiting toxicity for topotecan is neutropenia . Extensive prior radiation or bone marrow-suppressive chemotherapy increases the risk of myelosuppression

Renal clearance of topotecan is the major route of elimination of the drug and its metabolites

ANTHRACYCLINES

Anthracyclines are metabolized in the liver and excreted in the bile.

Doxorubicin

Doxorubicin is available in a standard form and a liposomal form

Administration & Dose

Standard Doxorubicin is administered at a dose of 30 to 75 mg/m2 IV- every 3 weeks

liposomal doxorubicin doses range from 20 to 60mg/m2 IV every 3 weeks intravenously

toxicity

Acute toxicities include myelosuppression, mucositis, alopecia, nausea, acute cardiotoxicity

the white blood cell count typically reaches a nadir at 10 to 14 days

Acute cardiotoxicity is reversible, and signs include tachycardia, hypotension, EKG changes

Doxorubicin is a potent vesicant and extravasation can lead to severe necrosis of skin and local tissues and longer infusions are recommended via a central venous catheter.

Acute treatment with ice and dimethyl sulfoxide may minimize tissue damage

Chronic cardiotoxicity is the most common type of anthracycline damage and is irreversible. Chronic cardiotoxicity peaks at 1 to 3 months but can occur even years after therapy

Sequential administration of paclitaxel followed by doxorubicin in breast cancer is associated with cardiomyopathy but reverse sequence of administration did not yield the same toxicitics.

When doxorubicin is given by a low-dose weekly regimen (10 to 20 mg/m2) or by slow continuous infusion 96 hours, cardiotoxicity decreases.

Dexrazoxane is a metal chelator that decreases the myocardial toxicity of doxorubicin

Other chronic toxicity of doxorubicin is secondary leukemia

Liposomal doxorubicin is associated with less nausea and vomiting and relatively mild myelosuppression and less cardiac toxicity

Liposomal doxorubicin causes hand-foot syndrome and an acute infusion reaction manifested by flushing, hypertension, edema, fever, chills, rash, bronchospasm.

Daunorubicin

It is FDA approved for the treatment of AML and ALL

Administration & Dose

Daunorubicin is typically administered intravenously 30 to 45 mg/m2 on 3 consecutive days

Daunorubicin has similar toxicities to doxorubicin

Daunorubicin is metabolized by the liver and undergoes substantial elimination by kidneys

Epirubicin

It is FDA approved for breast cancer but is also active in esophageal cancer, gastric cancer, ovarian cancer, small-cell carcinoma, soft tissue sarcoma and Hodgkin's lymphoma

Administration & Dose

Typical doses of epirubicin are 60 to 120 mg/m2 every 3 to 4 weeks given intravenously.

Toxicity

- Severe myelosuppression
- Epirubicin is also a vesicant
- nausea and vomiting -less than Adriamycin
- alopecia -less than Adriamycin
- cardiac toxicity -less than Adrimycin

Epirubicin is metabolized by the liver and excrete by liver and kidney

ANTHRACENEDIONES

Mitoxantrone

Mitoxantrone is approved for treatment of hormone-refractory prostate cancer and AML

Administration & Dose

- intravenously at a dose of 12 mg/m2 for 3 days in the treatment of AML
- intravenously at a dose 12 to 14 mg/m2 - every 3 weeks in prostate cancer

Toxicity

Dose-limiting toxicities involve myelosuppression and Cardiac toxicity

Actinomycins

Dactinomycin

Dactinomycin is FDA approved for Ewing's sarcoma, gestational trophoblastic neoplasm, metastatic testicular cancer, nephroblastoma and rhabdomyosarcoma

Administration & Dose

intravenously at doses of 12 to 15 mcg/kg for 5 days

Toxicity

Toxicities include myelosuppression, veno-occlusive disease of the liver, nausea, vomiting, alopecia, erythema, and acne, severe tissue necrosis in cases of extravasation

EPIPODOPHYLLOTOXINS

Etoposide

It is FDA approved for treatment of small-cell lung cancer and refractory testicular cancer

Administration & Dose

The intravenous form is generally administered at doses of 35 to 100 mg/m2 for 4 to 5 days every 3 to 4 weeks in combination therapy

The dose of oral etoposide is usually twice the intravenous dose.

Toxicity

The dose-limiting toxicity for etoposide is leukopenia

epipodophyllotoxins are associated with the greatest risk for of secondary malignancy (AML)

Teniposide

Teniposide is approved for A) pediatric ALL B) neuroblastoma C) non-Hodgkin's lymphoma

Administration & Dose

The typical dose ranges from 30 to 100 mg/m2 intravenously

Toxicity

the dose-limiting toxicity of teniposide is Myelosuppression

Teniposide is associated with greater frequency of hypersensitivity reactions than etoposide

PLATINUM ANALOGS

Cisplatin

One of most common antineoplasm

Administration & Dose

Intrapritoneal (ovary) or IV at dose of 50 to 75 mg/m2 every 3 to 4 weeks

The IP route of delivery is associated with ↑efficacy

protect against renal toxicity:

1) manitol (125 mg/KG may be mixed with drug)

2) Intravenous Thiosulfates in IP administration of cisplatin

Toxicity

- renal insufficiency with cation wasting
- nausea and vomiting,
- peripheral neuropathy
- auditory impairment
- myelosuppression with thrombocytopenia prominent
- seizures

Carboplatin

1) Ovarian cancer 2) Non-small cell lung cancer 3) cisplatin alternative

Administration & Dose

1) Practical method: 400mg carboplatin IV =100mg cis IV (4mg to 1mg)

2) calculation method: 4-6 AUC (Area Under the Curve) IV

AUC (carboplatin) = creatinine clearance + 25

Toxicity

1) Myelosuppresion
2) Alopecia
3) Peripheral neuropathy
4) Nausea
5) Liver Enzyme raising
6) Renal disorder

Carboplatin vs cisplatin

- Same range of drug interaction with Aminoglycosid
- Less nephrotoxic
- Less emetogenic.
- More toxic to bone marrow than cisplatin.

oxaliplatin

1) Colorectul cancer 2) Esophagus cancer 3) Gastric cancer

Administration & Dose

It is given intravenously at a dose of 85 to130 mg/m2 every 2-3 weeks

Toxicity

1) Hot flash
2) Chest pain → discontinue until symptoms removed
3) laryngopharyngeal dysesthesia → discontinue until symptoms removed
4) Abdomen pain
5) Dyspnea → discontinue until symptoms removed
6) Myelosuppression
7) diarrhea
8) peripheral neuropathy
9) moderate nausea and vomiting → level 3 anti-emesis

↑cumulative dose of cisplatin or carboplatin:
develops heavy metal renal toxicity lead, mercury (disassociation between Cr and GFR)

Emetic risk	Prevention of acute emesis D1	Prevention of delay emesis
High	5HT3-RA + Dexa + Aprepitant	Dexa (D 2-4) + Aprepitant (D2-3)
Moderate (Adria)	5HT3-RA + Dexa + Aprepitant	Aprepitant (D2-3)
Moderate(non Adria)	5HT3-RA + Dexa	Dexa (D2-3) or Aprepitant (D2-3)
low	Dexa or prochlorperzine	no prevention
minimal	As need	no prevention