Alkylating Agents

PHL 425

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Alkylating Agents

- Nitrogen Mustards
  - Cyclophosphamide
  - Ifosfamide
  - Melphalan
  - Chlorambucil

- Ethylenimines
  - Thiotepa

- Alkyl Sulfonates
  - Busulfan

- Nitrosoureas
  - Carmustine
  - Lomustine
  - Semustine
Alkylating Agents

Mechanism of Action

- Alkylate within DNA at the N7 position of guanine
- Resulting in miscoding through abnormal base-pairing with thymine or in depurination by excision of guanine residues, leading to strand breakage
- Cross-linking of DNA and ring cleavage may also occur
Nitrogen Mustards

- Cyclophosphamide
- Ifosfamide
- Mechlorethamine
- Melphalan
- Chlorambucil
Nitrogen Mustards

**Sulfur mustard**

**Cyclophosphamide**

**Nitrogen mustard**

**Ifosfamide**

**Melphalan**

**Chlorambucil**

*FIGURE 3* Sulfur mustard and nitrogen mustards.
Cyclophosphamide and ifosfamide are widely used in the treatment of hematological malignancies and solid tumours including:

- Breast
- Lung
- Prostate cancer
- Ovarian cancer
- Lymphomas and multiple myeloma.
Mechanism of Action

Figure 55–5. Mechanism of alkylation of DNA guanine. A bis(chloroethyl)amine forms an ethyleneimonium ion and a carbonium ion that react with a base such as N7 of guanine in DNA, producing an alkylated purine. Alkylation of a second guanine residue, through the illustrated mechanism, results in cross-linking of DNA strands.
Mechanism of Action

**FIGURE 4** Cross-linking of DNA by nitrogen mustards.
Mechanism of Action

- Cyclophosphamide and Ifosfamide are prodrugs and must be oxidized by CYP3A5 and CYP2B6 oxidase to acquire an antineoplastic activity through formation of Phosphoramide mustard and Ifosfamide Mustard which react with DNA to form covalent bonds, causing single-strand or double strand DNA breaks that lead to interstrand and intrastrand DNA cross-linking.
Phosphoramide Mustard and Ifosfamide Mustard react with DNA to form covalent bonds, causing single-strand or double strand DNA breaks that lead to interstrand and intrastrand DNA cross-linking.
Cyclophosphamide Metabolism

Cyclophosphamide $\xrightarrow{\text{P450}}$ 4-Hydroxycyclophosphamide $\xrightarrow{[\text{O}]}$ 4-Ketocyclophosphamide

Spontaneous reaction $\xleftarrow{\text{spontaneous}}$ Aldophosphamide $\xrightarrow{\text{ALDH}}$ Carboxyphosphamide

$\text{CH}_2=\text{CH} \cdot \text{C} \cdot \text{H}$

Acrolein

Hemorrhagic Cystitis
Ifosfamide Metabolism
Oxazaphosphorines-Induced Carnitine Deficiency

Chloroacetyl-CoA

Chloroacetyl-Carnitine

Excreted in urine

Thiodiglycolic Acid

Chloroacetaldehyde

CoA-SH

Long Chain Fatty Acid Oxidation

Fanconi Syndrome

CPT-I

Carnitine Deficiency
Toxicity of cyclophosphamide and Ifosfamide

1- hemorrhagic cystitis (Acroleine)
   Treated by coadministration MESNA

2- Neurotoxicity

3- Nephrotoxicity (FANCONI SYNDROME)

4- Cardiotoxicity
Nitrosoureas

- Carmustine
- Lomustine
- Semustine
- Streptozocin—naturally occurring sugar containing

🌟 All cross the blood brain barrier, so they are effective in treatment of brain tumours (GLIOMA) 🌟
GLIOMAS

- **Glioma** is a type of cancer that starts in the brain or spine. It is called a glioma because it arises from glial cells. The most common site of gliomas is the brain.

### Classification

- **By type of cell:** Gliomas are named according to the specific type of cell they most closely resemble. The main types of gliomas are:
  1. **Ependymomas** — ependymal cells
  2. **Astrocytomas** — astrocytes - Glioblastoma multiforme is the most common astrocytoma.
  3. **Oligodendrogliomas** — oligodendrocytes
  4. **Mixed gliomas**, such as **oligoastrocytomas**, contain cells from different types of glia.

- **By grade:**
  1. **Low-grade** gliomas are well-differentiated (not anaplastic); these are **benign** and portend a better prognosis for the patient.
  2. **High-grade** gliomas are undifferentiated or anaplastic; these are **malignant** and carry a worse prognosis.

- **By location:** Gliomas can be classified according to whether they are above or below a membrane in the brain called the **tentorium**. The tentorium separates the **cerebrum**, above, from the **cerebellum**, below.
  1. **Supratentorial:** Above the tentorium, in the cerebrum, mostly in adults (70%). Senator **Edward M. Kennedy's** brain tumor, for example was supratentorial, in the parietal area in the upper part of the left side of his brain, above the ear.[4]
  2. **Infratentorial:** Below the tentorium, in the cerebellum, mostly in children (70%)
Treatment of GLIOMAS

1- Surgery
2- Radiotherapy
3- Stereotactic Radiotherapy
4- Chemotherapy
5- Stereotactic Chemotherapy
Drug Therapy of Glioma

- Carmustine
- Stereotactic delivery of Carmustine
- Gliadel Carmustine wafer
- Temozolomide
- Biological Targeted Therapy
Temozolomide (Temodar)

- This medication is used to treat glioma (astrocytoma). The drug is taken by mouth in capsule form. Your full dose may contain two or more different strengths of temozolomide capsules. Take your dose at bedtime, with a full glass of water, on an empty stomach. Do not chew or open the capsules. If a capsule opens or breaks, be careful not to get the contents on the skin around your eyes, nose, or mouth. Temozolomide is usually given once daily for 5 days. The treatment may be repeated every 28 days.

- Temozolomide is in a class of drugs known as imidazotetrazine derivatives. It slows or stops the growth of cancer cells in your body. The length of treatment depends on how well your body responds to the treatment.
Antimetabolites

- Folic Acid Analogs
  - Methotrexate

- Purine Analogs
  - Mercaptoguanine

- Pyrimidine Analogs
  - Fluorouracil

Legend:
- Drug Class
- Sub-class
- Prototype Drug
Folic Acid Analogs

- Methotrexate
- Trimetrexate
- Pemetrexed
Folate

- An essential dietary factor, from which THF cofactors are formed which provide single carbon groups for the synthesis of precursors of DNA and RNA
- To function as a cofactor folate must be reduced by DHFR to THF
Methotrexate

Mechanism of Action

- The enzyme DHFR is the 1° site of action
- MTX prevents the formation of THF, causing an intracellular deficiency of folate coenzymes and accumulation of the toxic inhibitory substrate, DHF polyglutamate
- The one carbon transfer reactions for purine and thymidylate synthesis cease, interrupting DNA and RNA synthesis
Resistance