Alkylating Agents

- Alkylating agents are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in cells.
- They stop tumor growth by cross-linking guanine bases in DNA double-helix strands - directly attacking DNA. This makes the strands unable to uncoil and separate. As this is necessary in DNA replication, the cells can no longer divide.
- In addition, these drugs add methyl or other alkyl groups onto molecules where they do not belong which in turn inhibits their correct utilization by base pairing and causes a miscoding of DNA.

Alkylating agents are cell cycle-nonspecific. They work by three different mechanisms all of which achieve the same end result - disruption of DNA function and cell death:
- Attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA,
- DNA damage via the formation of cross-links (bonds between atoms in the DNA) which prevents DNA from being separated for synthesis or transcription, and
- The induction of mispairing of the nucleotides leading to mutations.

### Classes of Antineoplastic Agents

<table>
<thead>
<tr>
<th>Class of alkylating agent</th>
<th>Drugs in class</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nitrogen mustards</td>
<td>Melphalan</td>
<td>Hod, Lym, Leu, Lym, Solid, Soft, Mye</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>Lym, Lym, Solid, Soft, Mye</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>Mye</td>
</tr>
<tr>
<td>2. Ethyleneimines/ Methylmelamines</td>
<td>Thiotepa</td>
<td>Solid</td>
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<td></td>
<td>Hexamethylmelamine</td>
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<tr>
<td>3. Alkyl sulfonates</td>
<td>Busulfan</td>
<td>Lym</td>
</tr>
<tr>
<td>4. Nitrosoureas</td>
<td>Carmustine [BCNU]</td>
<td>Hod, Lym, Mye, Solid (Brain)</td>
</tr>
<tr>
<td></td>
<td>Lomustine</td>
<td>Lym, Lym, Solid, Soft, Mye, Solid (Brain)</td>
</tr>
<tr>
<td>5. Triazenes</td>
<td>Dacarbazine</td>
<td>Hod, Soft, Solid (Brain)</td>
</tr>
<tr>
<td></td>
<td>Temozolomide</td>
<td>Solid (Brain), Gliomas</td>
</tr>
</tbody>
</table>

### Alkylating Agents

- Melphalan [Nitrogen Mustard]
- Cyclophosphamide
- Ifosfamide
- Melphalan
- Chlorambucil

### Alkylating Agents

- Thiotepa
- Hexamethylmelamine
- Busulfan
- Carmustine [BCNU]
- Lomustine
- Dacarbazine
- Temozolomide

**Common mechanism of action:**
Conversion to an active aziridine.
Nucleophilic attack of unstable ring by electron donor (-SH, -N, =O) Alkylation
Antineoplastic Agents

Common mechanism of action:
Conversion to an active aziridine
Nucleophilic attack of unstable ring by electron donor [-SH, -N, =O]
Alkylation

Possible consequence 1:
Keto to Enol switch of nucleotide
Formation of G-T bonds & intrastrand bonds

Possible consequence 2:
Labilization of the imidazole ring of guanine
Excision of nucleotide.

Possible consequence 3:
[Nitrogen mustards]
Crosslinking of both DNA strands = DNA breakage.

Alkylating Agents

1) Nitrogen mustards
2) Other alkylation agents

Sulfur mustard
Mustard gas
Ypirite
Worls war I (1917)
Impurity smell like mustard / garlic

Metabolism of alkyl halides
Phase II conjug. glutathion

Rel. selective tox. to lymphoid tissue
(Hodkins disease, Lymphomas)
More water sol.

Bussulfan
Not reg. N
Mono or dialkylation
Better leav. gr, not 3-embered ring intermed of dimethyl sulfate

Thiotepa
Not reg. N

Even more reactive at low pH

Notes of Dr. Anil Mishra from www.anilmishra.name
**Mechlorethamine**

**Chemical Formula**
C₅H₁₁Cl₂N

**Trade Name**
Mustargen

**Dosage Forms**
- Powder
- Topical
- Injection, powder, for solution Intra venous

**Pharmacology**

Mechlorethamine also known as mustine, nitrogen mustard, and HN₂, is the prototype anticancer chemotherapeutic drug.

Successful clinical use of mechlorethamine gave birth to the field of anticancer chemotherapy.

The drug is an analogue of mustard gas and was derived from toxic gas warfare research.

It belongs to the group of nitrogen mustard alkylating agents.

Alkylating agents work by three different mechanisms all of which achieve the same end result - disruption of DNA function and cell death.

**Absorption**

Partially absorbed following intracavitary administration, most likely due to rapid deactivation by body fluids.

**Toxicity**

Symptoms of overexposure include severe leukopenia, anemia, thrombocytopenia, and a hemorrhagic diathesis with subsequent delayed bleeding may develop. Death may follow.

**Biotransformation**

Undergoes rapid chemical transformation and combines with water or reactive compounds of cells, so that the drug is no longer present in active form a few minutes after administration.

**Synthesis of Mechlorethamine**

2-{[2-Hydroxy-ethyl]-methyl}-amino-ethanol

Thionyl chloride

Mechlorethamine Hydrochloride

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**Notes of Dr. Anil Mishra from www.anilmishra.name**

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Cyclophosphamide

- **Chemical Formula**: C\(_7\)H\(_{15}\)Cl\(_2\)N\(_2\)O\(_2\)P
- **Trade Name**: Cytoxan, Neosar
- **Dosage Forms**:
  - Solution: Intravenous
  - Powder, for solution: Intravenous
  - Tablet: Oral

**Pharmacology**
- Cyclophosphamide is an antineoplastic in the class of alkylating agents and is used to treat various forms of cancer.
- **Toxicity**
  - Infection, myelosuppression, and cardiac toxicity
  - It is a "prodrug"; it is converted in the liver to active forms that have chemotherapeutic activity.
- The active metabolite is **4-hydroxycyclophosphamide**
- The main effect of cyclophosphamide is due to its metabolite phosphoramide mustard. This metabolite is only formed in cells which have low levels of ALDH.

**Activation and Metabolism of Cyclophosphamide**

**Side Effects**
- Chemotherapy-induced nausea and vomiting (CINV)
- Bone marrow suppression
- Stomach ache
- Diarrhea
- Darkening of the skin/nails
- Alopecia (hair loss)
- Lethargy

**Synthesis of Cyclophosphamide**

**Melphalan**

- **Chemical Formula**: C\(_{13}\)H\(_{18}\)Cl\(_2\)N\(_2\)O\(_2\)
- **Trade Name**: Alkeran
- **Dosage Forms**
  - Tablet: Oral

Notes of Dr. Anil Mishra from www.anilmishra.name
Melphalan

- Melphalan is an antineoplastic in the class of alkylating agents and is used to treat various forms of cancer.
- An alkylating nitrogen mustard that is used as an antineoplastic in the form of the levo isomer - melphalan, the racemic mixture - merphalan, and the dextro isomer - medphalan.
- Toxic to bone marrow, but little vesicant action; potential carcinogen.

Toxicity

- Vomiting,
- Ulceration of the mouth,
- Diarrhea, and
- Hemorrhage of the gastrointestinal tract;
- The principal toxic effect is bone marrow suppression.

Biotransformation

- Melphalan is not actively metabolised, it spontaneously degrades to mono and dihydroxy products.

Synthesis of Mephlan

\[ \text{2-Amino-3-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-phenyl]-propionic acid ethyl ester} \]

Hydrolysis

\[ \text{2-Amino-3-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-phenyl]-propionic acid ethyl ester} \]