# Cancer Chemotherapy

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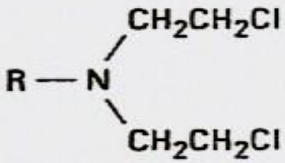
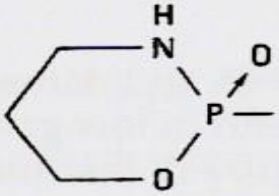
# Polyfunctional Alkylating Agents الادوية الاستخلابية متعددة الوظائف

- **Not cell cycle-specific.**
- **Work by transferring alkyl groups to various cellular constituents, mainly to DNA, leading to cell death.**
- **They also interact with sulfhydryl, amino, hydroxyl, carboxyl and phosphate groups of other cellular nucleophiles.**
- **DNA interactions can occur on a single strand or on both strands through cross-linking, i.e. bifunctional with two reactive groups.**

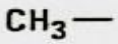
## BIS(CHLOROETHYL)AMINES



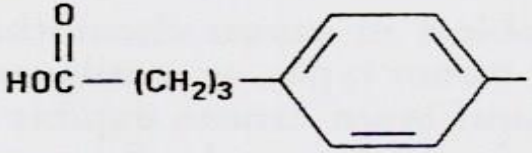
Where R is:



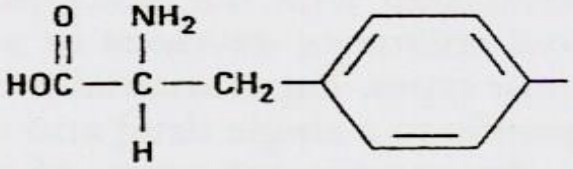
**Cyclophosphamide**



**Mechlorethamine**

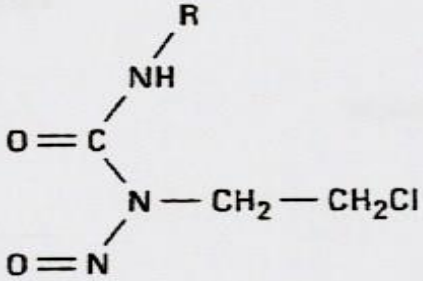


**Chlorambucil**



**Melphalan**

## NITROSOUREAS



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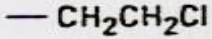
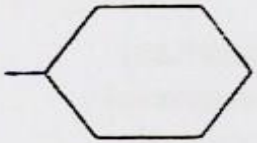
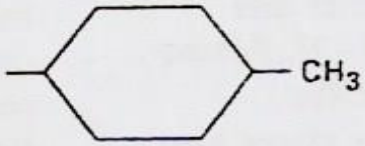


**BCNU**
**(carmustine)**

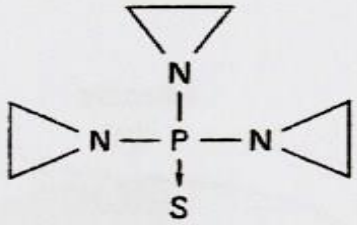


**CCNU**
**(lomustine)**

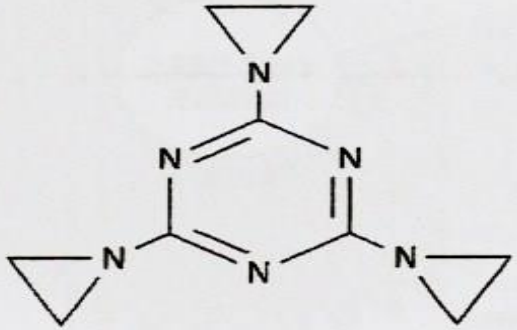


**Methyl-CCNU**
**(semustine)**

## AZIRIDINES

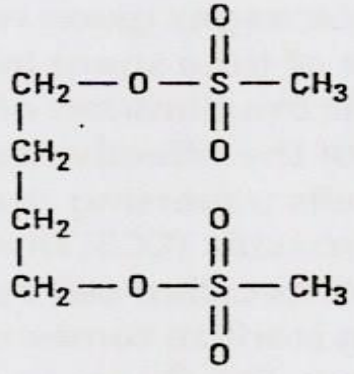


**Thiotepa**



**Triethylenemelamine**

## ALKYLSULFONATE



**Busulfan**

# Polyfunctional Alkylating Agents

- **Can cause acquired resistance and cross resistance , but not with nitrosureas.**
- **Direct vesicant effects.**
- **Nausea and vomiting.**

# Polyfunctional Alkylating Agents

- **Cyclophosphamide.**
- **Mechlorethamine.**
- **Chlorambucil.**
- **Melphalan.**
- **Thiotepa.**
- **Busulphan.**
- **Nitrosureas**

# Polyfunctional Alkylating Agents

- **Nitrosureas:**
- **Carmustine (BCNU).**
- **Lomustine (CCNU_.**
- **Semustine(methyl-CCNU).**
- **Streptozocin; for insulin-secreting islet cell carcinoma, also to induce diabetes in experimental animals.**
- **Not cross-resistant with other alkylating agents.**
- **Highly lipid soluble.**

# Polyfunctional Alkylating Agents

- **Platinum analogs**:
  - **Cisplatin:**
    - **Kills cells in all stages.**
    - **Binds DNA and inhibits synthesis and function.**
    - **Nephrotoxic, hydration is necessary.**
    - **Solid tumors.**

| Alkylating Agent | Single-Agent Dosage | Acute Toxicity | Delayed Toxicity |
|---|---|---|---|
| Mechlorethamine (nitrogen mustard) | 0.4 mg/kg IV in single or divided doses | Nausea and vomiting | Moderate depression of peripheral blood count; excessive doses produce severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency |
| Chlorambucil | 0.1–0.2 mg/kg/d orally; 6–12 mg/d | Nausea and vomiting | |
| Cyclophosphamide | 3.5–5 mg/kg/d orally for 10 days; 1 g/m$^2$ IV as single dose | Nausea and vomiting | |
| Melphalan | 0.25 mg/kg/d orally for 4 days every 4–6 weeks | Nausea and vomiting | |
| Thiotepa (triethylenethiophosphoramide) | 0.2 mg/kg IV for 5 days | Nausea and vomiting | |
| Busulfan | 2–8 mg/d orally; 150–250 mg/course | Nausea and vomiting | |
| Carmustine (BCNU) | 200 mg/m$^2$ IV every 6 weeks | Nausea and vomiting | Leukopenia, thrombocytopenia, and rarely hepatitis |
| Lomustine (CCNU) | 150 mg/m$^2$ orally every 6 weeks | Nausea and vomiting | |
| Altretamine | 10 mg/kg/d for 21 days | Nausea and vomiting | Leukopenia, thrombocytopenia, and peripheral neuropathy |
| Temozolomide | 150 mg/m$^2$ orally for 5 days every 28 days | Nausea and vomiting, headache and fatigue | Leukopenia, thrombocytopenia |
| Procarbazine | 50–200 mg/d orally | Nausea and vomiting | Bone marrow depression, central nervous system depression, leukemogenic |
| Dacarbazine | 300 mg/m$^2$ daily IV for 5 days | Nausea and vomiting | Bone marrow depression |
| Cisplatin | 20 mg/m$^2$/d IV for 5 days or 50–70 mg/m$^2$ as single dose every 3 weeks | Nausea and vomiting | Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction |
| Carboplatin | AUC 5–7 mg x min/mL | Nausea and vomiting | Myelosuppression; rarely: peripheral neuropathy, renal toxicity, and hepatic dysfunction |
| Oxaliplatin | 130 mg/m$^2$ IV every 3 weeks or 85 mg/m$^2$ IV every 2 weeks | Nausea and vomiting, laryngopharyngeal dysesthesias | Peripheral sensory neuropathy, diarrhea, myelosuppression, and renal toxicity |

# Antimetabolites

- **Utilize quantitative differences in metabolism of cancer cells from normal cells, that render them susceptible to a number of structural analogs.**
- **The most vulnerable pathways are those of nucleotide and nucleic acid synthesis.**

# Antimetabolites

## •Methotrexate (MTX):

- **Folic acid analog which binds to the active site of dihydrofolate reductase (DHFR), interfering with the synthesis of the reduced form that accepts one-carbon units.**
- **This will interrupt the *de novo* synthesis of thymidylate, purine nucleotides and the amino acids serine and methionine.**
- **This will interfere with the formation of DNA, RNA and key cellular proteins.**

- **Resistance to Methotrexate (MTX):**
  - **Decreased drug transport.**
  - **Decreased formation of cytotoxic MTX polyglutamate.**
  - **Synthesis of increased levels of DHFR through gene amplification.**
  - **Altered DHFR with reduced affinity for MTX.**
  - **Decreased accumulation of drug through activation of MDRP170 glycoprotein transporter.**

- **Leukovorine Rescue:**

- **The administration of the reduced folate leukovorine (5-formyltetrahydrofolate) to reverse the effects and toxicity of MTX.**
- **This will compete with methotrexate for DHFR**
- **Usually indicated in high dose methotrexate therapy to rescue normal cells.**

# Antimetabolites

- **Purine Antagonists:**
  - **6-Thiopurines:**
    - **6-Mercaptopurine (6-MP).**
    - **6-Thioguanine 6-TG).**

    **Inhibit several enzymes.**

    **6-MP metabolized by xanthine oxidase, so toxicity is enhanced by Allopurinol**

# Antimetabolites

- **Pyrimidine Antagonists:**
  - **5-Fluorouracil:**
    - **Most widely used agent in colorectal carcinoma, also stomach, breast, esophagus, liver, head and neck, and pancreas.**

***Table 55–3.*** Antimetabolites: Dosages and toxicities.

| Chemotherapeutic Agent | Single-Agent Dosage | Delayed Toxicity[1] |
|---|---|---|
| Capecitabine | 1250 mg/m$^2$/bid orally for 14 days followed by 1 week of rest. Repeat every 3 weeks. | Diarrhea, hand-and-foot syndrome, myelosuppression, nausea and vomiting |
| Cladribine | 0.09 mg/kg/d for 7 days by continuous IV infusion in sterile saline | Myelosuppression, nausea and vomiting, and immunosuppression |
| Cytarabine | 100 mg/m$^2$/d for 5–10 days, either by continuous IV infusion or SC every 8 hours. | Nausea and vomiting, bone marrow depression with leukopenia and thrombocytopenia, and cerebellar ataxia |
| Fludarabine | 25 mg/m$^2$/d for 5 days every 28 days (administer IV over 30 minutes) | Myelosuppression, immunosuppression, fever, myalgias, and arthralgias |
| 5-Fluorouracil | 15 mg/kg/d IV for 5 days by 24-hour infusion; 15 mg/kg weekly IV | Nausea, mucositis, diarrhea, bone marrow depression, and neurotoxicity |
| Gemcitabine | 1000 mg/m$^2$ IV weekly for up to 7 weeks followed by 1 week of rest | Nausea, vomiting, diarrhea, myelosuppression |
| 6-Mercaptopurine | 2.5 mg/kg/d orally | Myelosuppression, immunosuppression, and hepatotoxicity |
| Methotrexate | 2.5–5 mg/d orally (Rheumatrex); 10 mg intrathecally (Folex) once or twice weekly | Mucositis, diarrhea, bone marrow depression with leukopenia and thrombocytopenia |
| Pemetrexed | 500 mg/m$^2$ IV every 3 weeks | Myelosuppression, skin rash, mucositis, diarrhea, and fatigue |
| 6-Thioguanine | 2 mg/kg/d orally | Myelosuppression, immunosuppression, and hepatotoxicity |

[1]These drugs do not cause acute toxicity.

# Plant Alkaloids

**Vinblastine:**

- **Periwinkle plant *Vinca rosea.***
- **Inhibits tubulin polymerization, disrupting assembly of microtubules, which are important part of the cytoskeleton and the mitotic spindle.**
- **This effect results in mitotic arrest and death of the cell.**

# Plant Alkaloids

**Vincristine:**

- **Similar actions but different clinical activities and toxicity.**
- **Pediatric tumors.**
- **Neurotoxicity**
- **Milder myelosuppression.**
- **SIADH**

# Antitumor Antibiotics

- **Products of various strains of the soil microbe *Streptomyces.***
- **Bind to DNA through intercalation between specific bases and block the synthesis of RNA, DNA or both, cause DNA strand scission and interference with cell replication.**

# Antitumor Antibiotics

## Anthracyclines:

**Daunorubicin.**

**Doxorubicin " Adriamycin"**

**Idarubicin.**

**Epirubicin**

- **Very widely used.**
- **Inhibit topoisomerase II.**
- **Intercalate with DNA.**
- **Bind to membranes to alter fluidity and ion transport.**
- **Generate semiquinone and oxygen free radicals leading to cardiotoxicity.**

# Antitumor Antibiotics

**Anthracyclines:**

- **IV.**
- **Metabolized and excreted through the liver.**
- **Given on every 3-week schedule.**
- **Or, as low-dose weekly,**
- **Or, 72-96 hour continuous infusion.**

# Antitumor Antibiotics

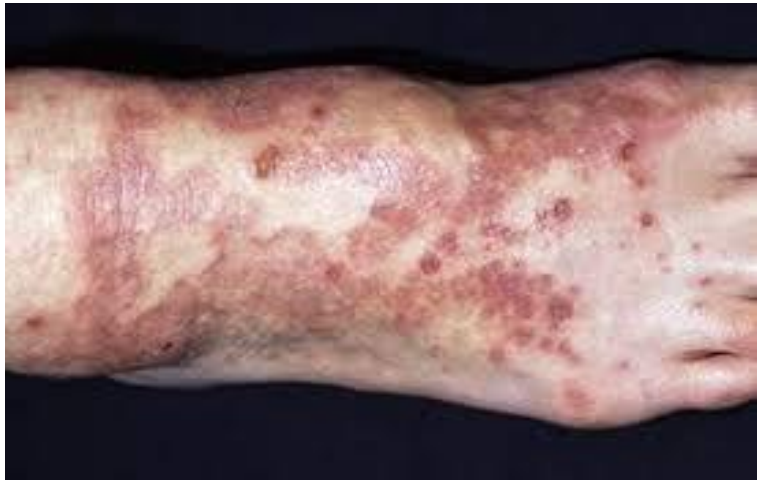
**Anthracyclines:**

- **Important anticancer drugs.**
- **Cancers of breast, endometrium, ovary, testicles, thyroid, stomach, bladder, liver, lung, soft tissue sarcomas, in childhood cancers and in hematologic malignancies.**

# Antitumor Antibiotics

## Anthracyclines:

- **Myelosuppression.**
- **Mucositis, sometimes is dose-limiting.**
- **"Radiation Recall Reaction":** a severe skin reaction that occurs when certain chemotherapy drugs are administered during or soon after radiation treatment.



# Antitumor Antibiotics

- **Cardiotoxicity:**
  - **Acute: first 2-3 days.**
    - **Arrhythmias and ECG changes, pericarditis and myocarditis.**
  - **Chronic: dose dependent.**
    - **Cardiomyopathy and heart failure.**
    - **Results from increased production of free radicals.**
    - **Reduced by weekly or continuous treatment.**
    - **Iron chelation treatment may reduce it.**

# Hormonal Agents

- **Estrogen Inhibitor:**
  - **Tamoxifen:**
    - **Competitive partial agonist-inhibitor of estrogen and binds to estrogen receptor of estrogen-sensitive tumors.**
    - **Extremely useful for both early and metastatic breast carcinoma.**
    - **Also as chemopreventive agent in women at high risk.**
    - **Endometrial cancer.**
    - **Oral and vey safe.**

# Hormonal Agents

- **Androgen Inhibitors:**
  - **Flutamide.**
  - **Bicalutamide.**
    - **Are nonsteroidal antiandrogen agents.**
    - **Oral.**
    - **Used in combination with radiation therapy for early-stage prostate cancer and metastatic cancer.**

# Hormonal Agents

- **Gonadotrpin-releasing Hormone Agonists:**
  - **Leuprolide.**
  - **Goserelin.**
    - **Are synthetic peptide analogs.**
    - **Given as depot preparations leading to transient release of FSH and LH followed by marked inhibition.**
    - **Indicated for advanced prostate cancer.**
    - **Cause hot flushes, impotence and gynecomastia.**

# Hormonal Agents

- **Aromatase Inhibitors:**
  - **Aminoglutethimide:**
    - **Nonsteroidal inhibitor of corticosteroid synthesis at the first step( cholesterol ---- pregnenolone).**
    - **Also inhibits extra-adrenal synthesis of estrone and estradiol.**
    - **Also; in body fat; inhibits aromatase enzyme that converts the adrenal androgen androstenedione to estrone.**
    - **Primarily used in metastatic breast carcinoma with significant estrogen or progesterone receptor expression.**
    - **Also effective in advanced prostate cancer.**
    - **Normally given with hydrocortisone**

***Table 55–5.*** Hormonally active agents: Dosages and toxicities.

| Drug | Usual Adult Dosage | Acute Toxicity | Delayed Toxicity |
|---|---|---|---|
| **Antiandrogen** | | | |
| Flutamide | 250 mg/tid orally | Mild nausea | Hot flushes, transient elevations in liver function tests |
| **Antiestrogen** | | | |
| Tamoxifen | 20 mg/d orally | Transient flare of tumor symptoms | Menopausal symptoms, fluid retention and edema, thromboembolic events, increased incidence of endometrial hyperplasia and cancer |
| **Progestins** | | | |
| Megestrol acetate | 40 mg orally 4 times daily | None | Fluid retention |
| **Adrenocorticosteroids** | | | |
| Hydrocortisone | 40–200 mg/d orally | None | Fluid retention, hypertension, diabetes, increased susceptibility to infection, moon facies |
| Prednisone | 20–100 mg/d orally | None | |
| **Gonadotropin-releasing hormone agonists** | | | |
| Goserelin acetate | 3.6 mg SC monthly | Transient flare of tumor symptoms, pain at injection site | Hot flushes, impotence, gynecomastia |
| Leuprolide | 7.5 mg SC monthly | Transient flare of tumor symptoms, pain at injection site | Hot flushes, impotence, gynecomastia |
| **Aromatase inhibitors** | | | |
| Aminoglutethimide | 250 mg orally twice daily and hydrocortisone 20 mg twice daily | Fatigue, mild nausea | Skin rash, adrenal insufficiency, myelosuppression |
| Anastrozole | 1 mg orally daily | Mild nausea, headache | Fatigue, hot flushes, arthralgias |
| Exemestane | 25 mg orally daily | Mild nausea, headache | Fatigue, hot flushes |
| Letrozole | 2.5 mg orally daily | Mild nausea, headache | Fatigue, hot flushes, arthralgias |

***Table 55–6.*** Miscellaneous anticancer drugs: Dosages and toxicities.

| Drug | Usual Dosage | Acute Toxicity | Delayed Toxicity |
|---|---|---|---|
| Arsenic trioxide | 0.15 mg/kg/d IV for 60 days as induction therapy; 0.15 mg/kg/d IV for 5 days per week for a total of 5 weeks as consolidation therapy | Headache and lightheadedness | Fatigue, cardiac dysrhythmias, fever, dyspnea, fluid retention and weight gain |
| Asparaginase | 20,000 IU/$m^2$ daily IV for 5–10 days | Nausea, fever, and allergic reactions | Hepatotoxicity, mental depression, pancreatitis |
| Bevacizumab | 5 mg/kg IV every 2 weeks | Hypertension, infusion reaction | Arterial thromboembolic events, gastrointestinal perforations, wound healing complications |
| Cetuximab | 400 mg/$m^2$ IV loading dose; 250 mg/$m^2$ IV weekly | Infustion reaction | Skin rash, interstitial lung disease |
| Erlotinib | 150 mg/d orally | Diarrhea | Skin rash, interstitial lung disease |
| Gefitinib | 250 mg/d orally | Hypertension, diarrhea | Skin rash, interstitial lung disease |
| Imatinib | 400–600 mg/d orally | Nausea and vomiting | Fluid retention with ankle and periorbital edema, diarrhea, myalgias |
| Hydroxyurea | 300 mg/$m^2$ orally for 5 days | Nausea and vomiting | Bone marrow depression |
| Mitoxantrone | 10–12 mg/$m^2$ IV every 3–4 weeks | Nausea | Bone marrow depression, occasional cardiac toxicity, mild alopecia |
| Trastuzumab[1] | 4 mg/kg IV loading dose; 2 mg/kg/wk as maintenance | Nausea and vomiting, infusion-related hypersensitivity reaction | Cardiomyopathy, myelosuppression, pulmonary toxicity |

[1]This monoclonal antibody is described in Chapter 56: Immunopharmacology.