Cancer Chemotherapy

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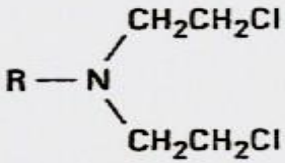
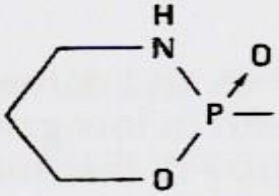
Polyfunctional Alkylating Agents
الادوية الاستخلابية متعددة الوظائف

- 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.

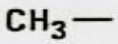
BIS(CHLOROETHYL)AMINES



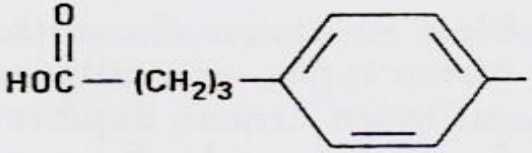
Where R is:



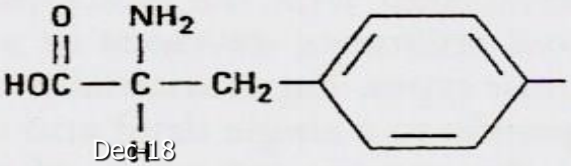
Cyclophosphamide



Mechlorethamine

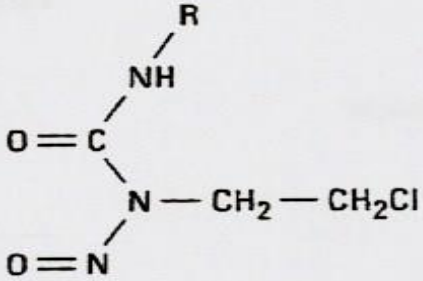


Chlorambucil

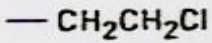


Melphalan

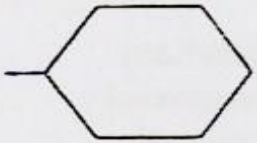
NITROSOUREAS



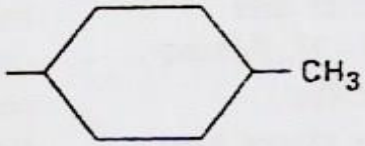
Where R is:



BCNU
(carmustine)

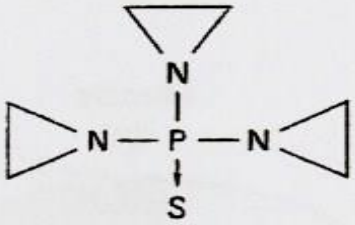


CCNU
(lomustine)

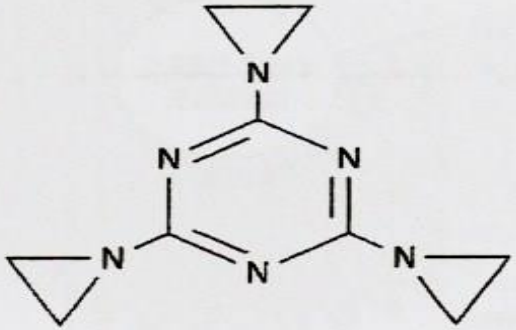


Methyl-CCNU
(semustine)

AZIRIDINES

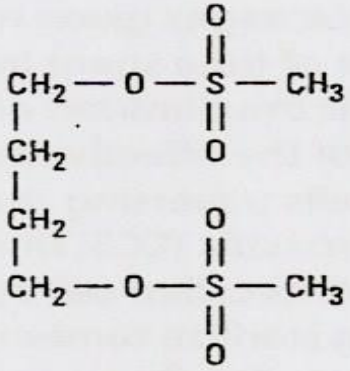


Thiotepa



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 (triethylenethio-phosphoramide)	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.