Cancer Chemotherapy –I

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Pharmacology of Antineoplastic Agents

1. Antineoplastic Agents: classification
    a. Cell Cycle Specific (CCS) agents
    b. Cell Cycle Non-Specific (CCNS) agents
    c. Miscellaneous (e.g., antibodies) agents

4. Mechanisms of action
5. Side Effects
6. Drug Resistance

1. Antineoplastic Agents

    a. Cell Cycle Specific (CCS) agents
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    c. Miscellaneous (e.g., antibodies) agents

Cancer Therapeutic Modalities (classical)

1. Surgery
2. Radiation

1/3 of patients without metastasis
Respond to surgery and radiation.

If diagnosed at early stage,
close to 50% cancer
could be cured.

3. Chemotherapy

50% patients will undergo chemotherapy,
to remove micrometastasis. However,
chemotherapy is able to cure only about 10-15%
of all cancer patients.

New types of cancer treatment

Hormonal Treatments: These drugs are designed to prevent cancer cell growth by preventing the cells from receiving signals necessary for their continued growth and division. E.g., Breast cancer – tamoxifen after surgery and radiation

Specific Inhibitors: Drugs targeting specific proteins and processes that are limited primarily to cancer cells or that are much more prevalent in cancer cells.

Antibodies: The antibodies used in the treatment of cancer have been manufactured for use as drugs. E.g., Herceptin, avastin

Biological Response Modifiers: The use of naturally occuring, normal proteins to stimulate the body's own defenses against cancer. E.g., Abciximab, rituxmab

Vaccines: Stimulate the body's defe... proteins found on or produced by cancer cells. By administering ... the treatment aims to increase the response of the body against the cancer cells.

Cancer Chemotherapy

C. Malignancies which respond favorably to chemotherapy:

1. choriocarcinoma,
2. Acute leukemia,
3. Hodgkin's disease,
4. Burkitt's lymphoma,
5. Wilms' tumor,
6. Testicular carcinoma,
7. Ewing's sarcoma,
8. Retinoblastoma in children,
9. Diffuse histiocytic lymphoma and
10. Rhabdomyosarcoma.

D. Antineoplastic drugs are most effective against rapidly dividing tumor cells.

General rules of chemotherapy

- **Aggressive high-dose chemotherapy**
  - **Dose**- limiting is toxicity towards normal cells
  - **Cyclic regimens** - repeated administrations with appropriate intervals for regeneration of normal cells (e.g., bone marrow cells)
  - **Supportive therapy -** to reduce toxicity
    - hematotoxicity – bone marrow transplantation, hematopoietic growth factors
    - Specific antagonists: antifolate (methotrexate) – folate (leucovorin)
    - MESNA - donor of –SH groups, decreased urotoxicity of cyclophosphamide. Detoxifying agent.
    - dexrazoxane: chelates iron, reduced anthracycline cardiotoxicity
    - amifostine: reduces hematotoxicity, ototoxicity and neurotoxicity of alkylating agents

General rules of chemotherapy

- Combination of several drugs with different mechanisms of action, different resistance mechanisms, different dose-limiting toxicities.

- **Adjuvant therapy:** Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

- **Neoadjuvant therapy:** Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

General rules of chemotherapy

- Supportive therapy:
  - -Antiemetics (5-HT_3 -antagonists)
  - -Antibiotic prophylaxis and therapy (febrile neutropenia)
  - -Prophylaxis of urate nephropathy (allopurinol)
  - -Enteral and parenteral nutrition
  - -Pain – analgesic drugs
  - -Psychological support

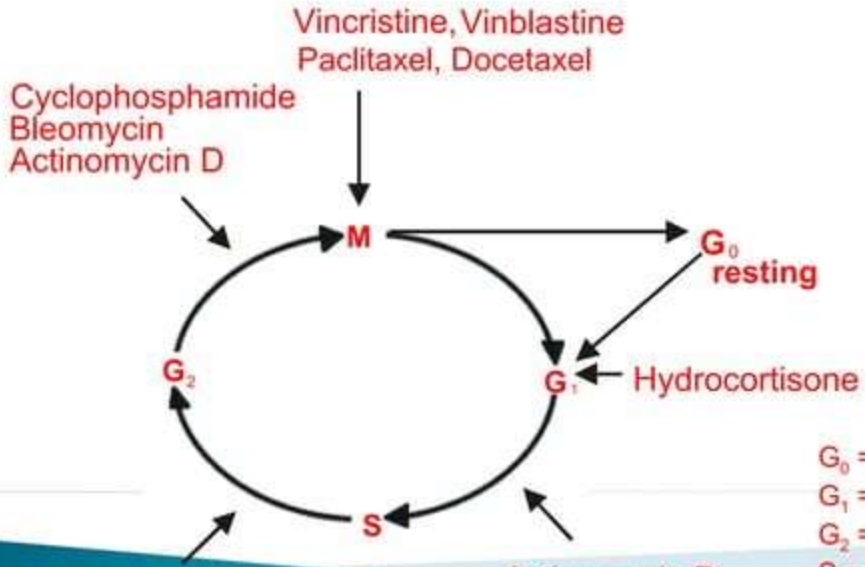
Antineoplastic Agents

Alkylating agents	Topoisomerase inhibitors	Antimetabolites	Molecularly targeted
busulfan	dactinomycin	cytarabine	erlotinib
carboplatin	daunomycin	clofarabine	imatinib
carmustine	doxorubicin	fludarabine	sorafenib
cisplatin	etoposide	gemcitabine	sunitinib
cyclophosphamide	etoposide phosphate	mercaptopurine	tretinoin
dacarbazine	idarubicin	methotrexate	Herceptin
ifosfamide	irinotecan	nelarabine	**Miscellaneous**
lomustine	liposomal daunomycin	thioguanine	arsenic trioxide
mechlorethamine	liposomal doxorubicin	**Tubulin binders**	asparaginase
melphalan	mitoxantrone	docetaxel	bleomycin
oxaliplatin	teniposide	ixabepilone	dexamethasone
procarbazine	topotecan	vinblastine	hydroxyurea
temozolomide		vincristine	
thiotepa		vinorelbine	PEG-asparaginase
		paclitaxel	prednisone

Table 55–1. Cell cycle effects of major classes of anticancer drugs.

Cell Cycle–Specific (CCS) Agents	Cell Cycle–Nonspecific (CCNS) Agents
Antimetabolites	**Alkylating agents**
Capecitabine	Busulfan
Cladribine	Carmustine
Cytarabine	Cyclophosphamide
Fludarabine	Lomustine
5-Fluorouracil (5-FU)	Mechlorethamine
Gemcitabine	Melphalan
6-Mercaptopurine (6-MP)	Thiotepa
Methotrexate (MTX)	**Anthracyclines**
6-Thioguanine (6-TG)	Daunorubicin
Antitumor antibiotic	Doxorubicin
Bleomycin	Epirubicin
Epipodophyllotoxins	Idarubicin
Etoposide	Mitoxantrone
Teniposide	**Antitumor antibiotics**
Taxanes	Dactinomycin
Albumin-bound paclitaxel	Mitomycin
Docetaxel	**Camptothecins**
Paclitaxel	Irinotecan
Vinca alkaloids	Topotecan
Vinblastine	**Platinum analogs**
Vincristine	Carboplatin
Vinorelbine	Cisplatin
	Oxaliplatin

Cell cycle specificity of Anti-Neoplastic Agents



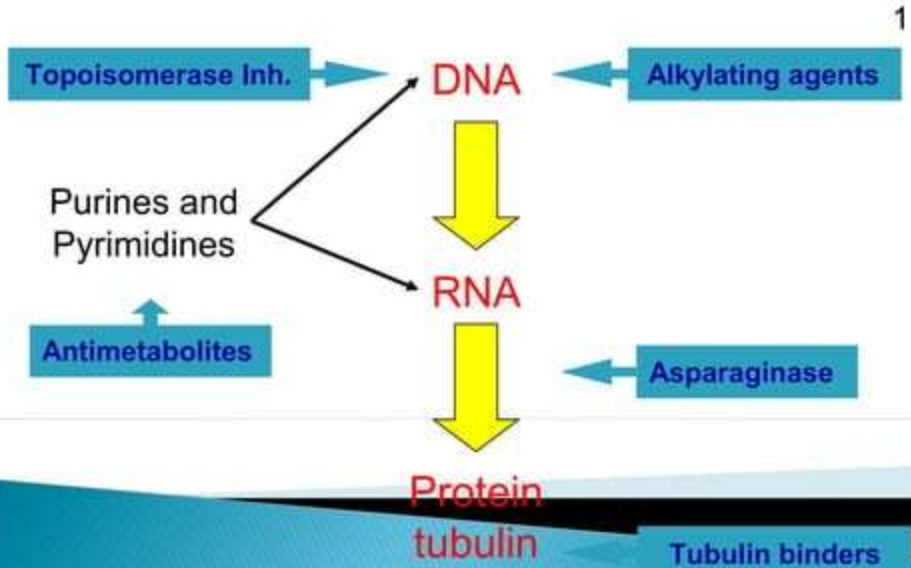
G_0 = resting phase
G_1 = pre-replicative phase
G_2 = post-replicative phase
S = DNA synthesis
M = mitosis or cell division

Pharmacology of Antineoplastic Agents

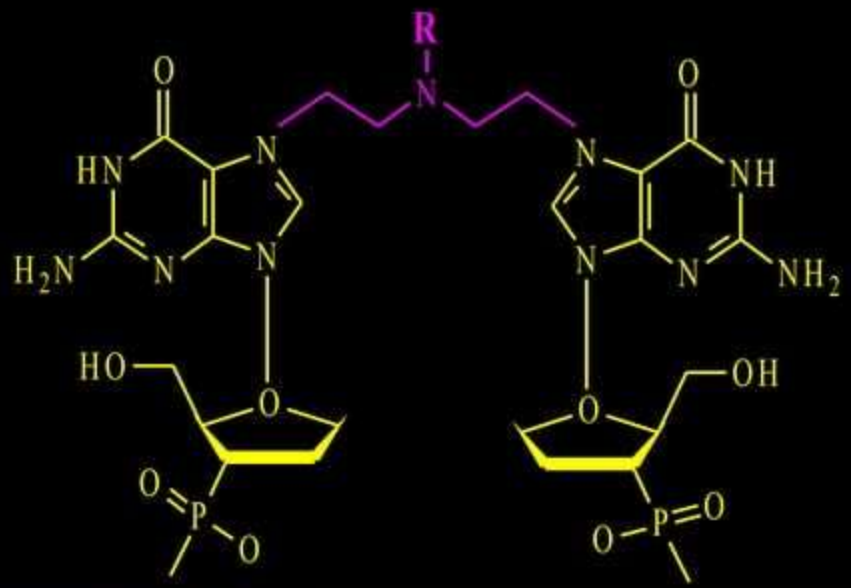
PART II

4. Mechanisms of action
5. Side Effects
6. Drug Resistance

Chemotherapy: Mechanisms of Action



An Example of DNA Crosslinking



Crosslinking: Joining two or more molecules by a ... either occur in the same strand (intrastrand crosslink) or in the opposite strands of the DNA (interstrand crosslink). Crosslinks also occur between DNA and protein. DNA replication is blocked by crosslinks, which causes replication arrest and cell death if the crosslink is not repaired.

Cyclophosphamide

Cyclophosphamide is an alkylating agent. It is a widely used as a DNA crosslinking and cytotoxic chemotherapeutic agent.

•It is given orally as well as intravenously with efficacy.

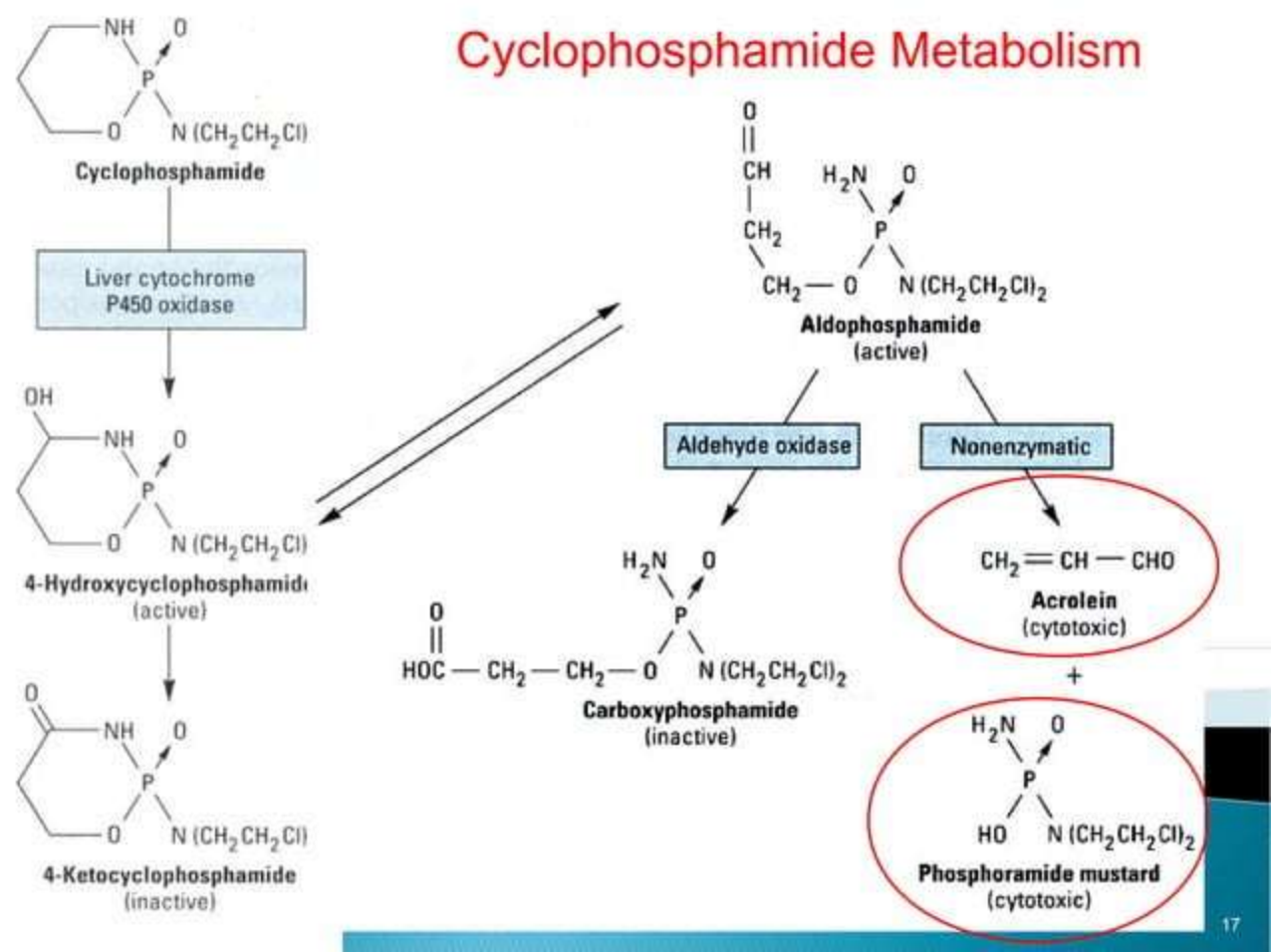
•It is inactive in parent form, and must be activated to cytotoxic form by liver CYT450 liver microsomaal system to 4-Hydroxycyclophamide and Aldophosphamide.

•4-Hydroxycyclophamide and Aldophosphamide are delivered to the dividing normal and tumor cells.

•Aldophosphamide is converted into acrolein and phosphoramide mustard.

•They crosslink DNAs resulting in inhibition of DNA synthesis

Cyclophosphamide Metabolism



Cyclophosphamide

Clinical Applications:

1. Breast Cancer
2. Ovarian Cancer
3. Non-Hodgkin's Lymphoma
4. Chronic Lymphocytic Leukemia (CLL)
5. Soft tissue sarcoma
6. Neuroblastoma
7. Wilms' tumor
8. Rhabdomyosarcoma

Cyclophosphamide

Major Side effects

1. Nausea and vomiting
2. Decrease in PBL count
3. Depression of blood cell counts
4. Bleeding
5. Alopecia (hair loss)
6. Skin pigmentation
7. Pulmonary fibrosis

Ifosphamide

Mechanisms of Action

Similar to cyclophosphamide

Application

1.Germ cell cancer,

2.Cervical carcinoma,

3.Lung cancer

4.Hodgkins and non-Hodgkins lymphoma

5.Sarcomas

Major Side Effects

Similar to cyclophosphamide

A. Alkylating agents

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
a. Nitrogen Mustards				
A. Mechlorethamine	DNA cross-links, resulting in inhibition of DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma	Must be given Orally	Nausea and vomiting, decrease in PBL count, BM depression, bleeding, alopecia, skin pigmentation, pulmonary fibrosis
B. Cyclophosphamide	Same as above	Breast, ovarian, CLL, soft tissue sarcoma, WT, neuroblastoma	Orally and I.V.	Same as above
C. Chlorambucil	Same as above	Chronic lymphocytic leukemia	Orally effective	Same as above
D. Melphalan	Same as above	Multiple myeloma, breast, ovarian	Orally effective	Same as above
E. Ifosfamide	Same as above	cervical carcinoma, lung, Hodgkins and non-Hodgkins lymphoma, sarcomas	effective	

A. Alkylating agents

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
b. Alkyl Sulfonates				
A. Busulfan	Atypical alkylating agent.	Chronic granulocytic leukemia	Orally effective	Bone marrow depression, pulmonary fibrosis, and hyperuricemia
c. Nitrosoureas	**1. Mechanism of Action**	**2. Clinical application**	**3. Route**	**4. Side effects**
A. Carmustine	DNA damage, it can cross blood-brain barrier	Hodgkins and non-Hodgkins lymphoma, brain tumors, G.I. carcinoma	Given I.V. must be given slowly.	Bone marrow depression, CNS depression, renal toxicity
B. Lomustine	Lomustine alkylates and crosslinks DNA, thereby inhibiting DNA and RNA synthesis. Also carbamoylates DNA and proteins, resulting in inhibition of DNA and RNA synthesis and disruption of RNA processing. Lomustine is lipophilic and crosses the blood-brain barrier	Hodgkins and non-Hodgkins lymphoma, malignant melanoma and epidermoid carcinoma of lung	Orally effective	Nausea and vomiting, Nephrotoxicity, nerve dysfunction
C. Streptozotocin	DNA damage	pancreatic cancer	Given I.V.	Nausea and vomiting,

A. Alkylating agents

d. Ethylenimines	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Triethylene thiophosphoramide (Thio-TEPA)	DNA damage, Cytochrome P450	Bladder cancer	Given I.V.	Nausea and vomiting, fatigue
B. Hexamethylmelamine (HMM)	DNA damage	Advanced ovarian tumor	Given orally after food	Nausea and vomiting, low blood counts, diarrhea

d. Triazenes	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Dacarbazine (DTIC)	Blocks, DNA, RNA and protein synthesis	Malignant Melanoma, Hodgkins and non-Hodgkins lymphoma	Given I.V.	Bone marrow depression, hepatotoxicity, neurotoxicity, bleeding, bruising, blood clots, sore mouths.

Summary

A. Alkylating agents

1. Interfere with cell division in all rapidly proliferating tissues

2. Most susceptible tissues are hematopoietic and GI epithelium

3. Mechanism of action: react with body fluid to form carbonium ions which bind guanine residue of DNA; such binding could result in:

   a. Miscoding of DNA
   b. Imidazole ring cleavage
   c. Excision of guanine residue producing DNA chain scission
   d. Cross linkages between DNA strands; this effect thought to be primary mode of cytotoxic action

4. Development of resistance possibly due to

   a. Decreased cellular permeability
   b. Production of substances which compete with DNA for alkylation
   c. Increased rate of DNA repair

5. Toxic side effects

   a. Bone marrow depression
   b. Nausea and vomiting especially when given I.V.
   c. Can get additive effects when used with ionizing radiation and antimetabolites

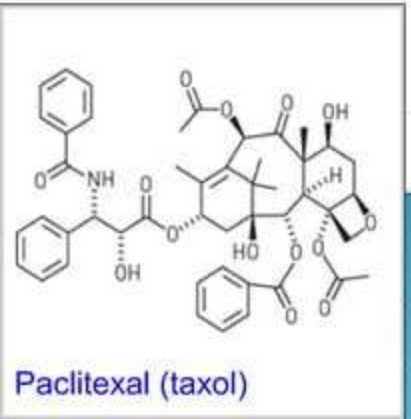
Tubulin Binding Agents

Vincristine

Polymerization

tubulin β α

e.g., Vincristine, Vinblastine, Vindesine Vinorelbine: Inhibition of mitotic spindle formation by binding to tubulin.
M-phase of the cell cycle.



Paclitexal (taxol)

Depolymerization

e.g., Paclitexal: binds microtubule formation and retards disassembly; results in mitotic arrest.

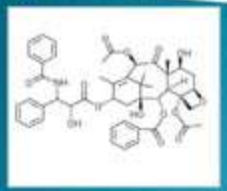
B. Natural Products

1. Antimitotic Drugs

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Vincristine	Cytotoxic: Inhibition of mitotic spindle formation by binding to tubulin. M-phase of the cell cycle.	Metastatic testicular cancer, Hodgkins and non-Hodgkins lymphoma, Kaposi's sarcoma, breast carcinoma, chriocarcinoma, neuroblastoma	I.V.	Bone marrow depression, epithelial ulceration, GI disturbances, neurotoxicity
B. Vinblastine	Methylates DNA and inhibits DNA synthesis and function	Hodgkins and non-Hodgkins lymphoma, brain tumors, breast carcinoma, chriocarcinoma, neuroblastoma	I.V.	Nausea and vomiting, neurotoxicity, thrombocytosis, hyperuricemia.

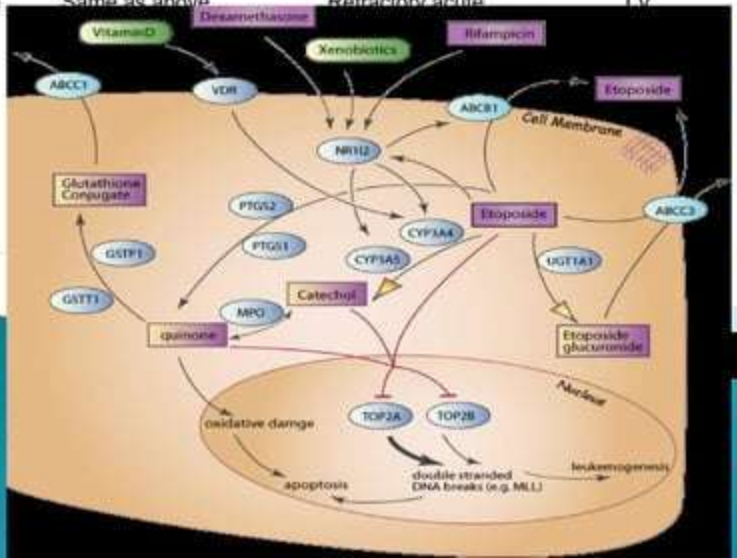
2. Antimitotic Drugs

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
Paclitaxel (Taxol)	Cytotoxic: binds to tubulin, promotes microtubule formation and retards disassembly; mitotic arrest results	Melanoma and carcinoma of ovary and breast	I.V.	Myelodepression and neuropathy



3. Epipodophyllotoxins (These are CCS) Act on Topoisomerase II

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
A. Etoposide	Binds to and inhibits Topoisomerase II and its function. Fragmentation of DNA leading to cell death, apoptosis.	Testicular cancer, small-cell lung carcinoma, Hodgkin lymphoma, carcinoma of breast, Kaposi's sarcoma associated with AIDS	I.V.	Myelosuppression, alopecia
B. Teniposide	Same as above	Refractory acute	I.V.	Myelosuppression,



Accumulation of single- or double-strand DNA breaks, the inhibition of DNA replication and transcription, and apoptotic cell death.

Etoposide acts primarily in the G_2 and S phases of the cell cycle

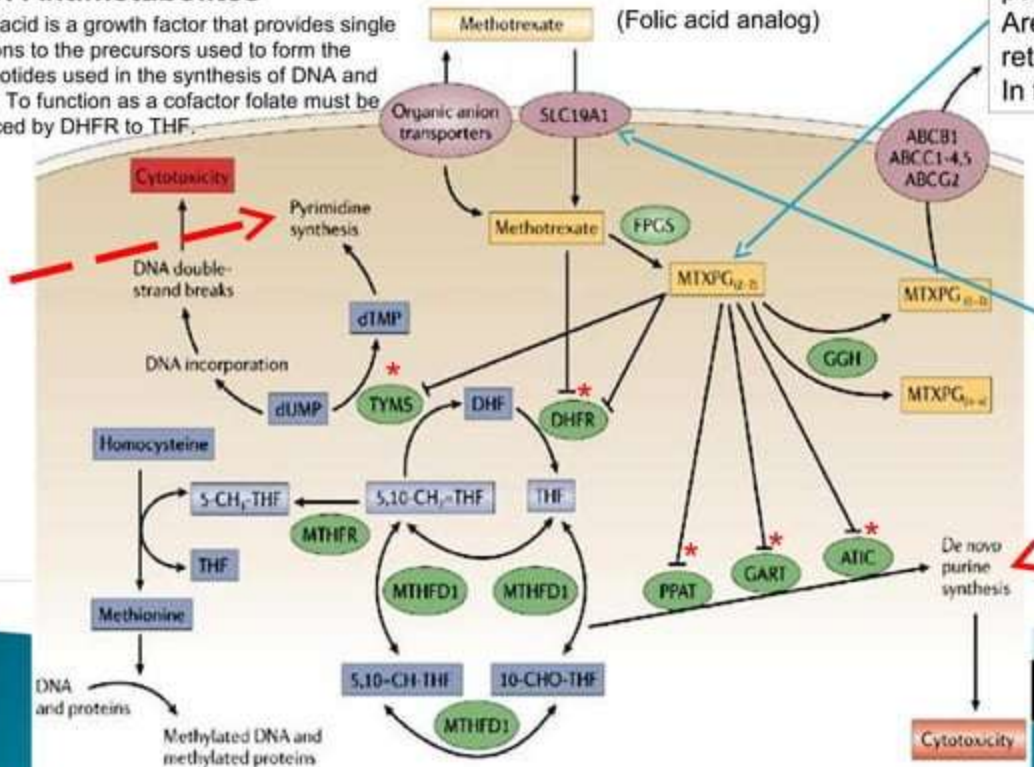
4. Antibiotics (CCS)

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
a. Dactinomycin (ACTINOMYCIN D)	It binds to DNA and inhibits RNA synthesis, impaired mRNA production, and protein synthesis	Rhabdomyosarcoma and Wilm's tumor in children; choriocarcinoma (used with methotrexate	I.V.	Bone marrow depression, nausea and vomiting, alopecia, GI disturbances, and ulcerations of oral mucosa
b. Daunorubicin (CERUBIDIN)	inhibit DNA and RNA synthesis	Acute lymphocytic/granulocytic leukemias; treatment of choice in nonlymphoblastic leukemia in adults when given with cytarabine	I.V.	Side effects: bone marrow depression, GI disturbances and cardiac toxicity (can be prevented by dexrazoxane)
Doxorubicin (ADRIAMYCIN)	inhibit DNA and RNA synthesis	Acute leukemia, Hodgkin's disease, non Hodgkin's lymphomas (BACOP regimen), CA of breast & ovary, small cell CA of lung, sarcomas, best available agent	I.V.	Cardiac toxicity, Doxorubicin mainly affects the heart muscles, leading to tiredness or breathing trouble when climbing stairs or walking, swelling of the feet .
c. Bleomycin (BLENOXANE)	fragment DNA chains and inhibit repair	Germ cell tumors of testes and ovary, e.g., testicular carcinoma (can be curative when used with vinblastine & cisplatin), squamous cell carcinoma	Given I.V. or I.M.	Mucocutaneous and pulmonary fibrosis; bone marrow depression much less than other antineoplastics

Inhibit DNA and RNA syntheses

C. Antimetabolites

Folic acid is a growth factor that provides single carbons to the precursors used to form the nucleotides used in the synthesis of DNA and RNA. To function as a cofactor folate must be reduced by DHFR to THF.



MTX polyglutamates Are selectively retained In tumor cells.

Reduced Folate Carrier protein

MTX Kills cells during S-phase

C. Antimetabolites

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
1. Methotrexate	inhibits formation of FH4 (tetrahydrofolate) from folic acid by inhibiting the enzyme dihydrofolate reductase (DHFR); since FH4 transfers methyl groups essential to DNA synthesis and hence DNA synthesis blocked.	Choriocarcinoma, acute lymphoblastic leukemia (children), osteogenic sarcoma, Burkitt's and other non-Hodgkin's lymphomas, cancer of breast, ovary, bladder, head & neck	Orally effective as well as given I.V.	bone marrow depression, intestinal lesions and interference with embryogenesis. Drug interaction: aspirin and sulfonamides displace methotrexate from plasma

	1. Mechanism of Action	2. Clinical application	3. Route	4. Side effects
2 Pyrimidine Analogs: Cytosine Arabinoside	inhibits DNA synthesis	most effective agent for induction of remission in acute myelocytic leukemia; also used for induction of remission acute lymphoblastic leukemia, non-Hodgkin's lymphomas; usually used in combination chemotherapy	Orally effective	bone marrow depression
	1. Mechanism of Action	**2. Clinical application**	**3. Route**	**4. Side effects**
2 Purine analogs: 6-Mercaptopurine (6-MP) and Thioguanine	Blocks DNA synthesis by inhibiting conversion of IMP to AMPS and to XMP as well as blocking conversion of AMP to ADP; also blocks first step in purine synthesis. Feedback inhibition blocks DNA synthesis by inhibiting conversion of IMP to XMP as well as GMP to GDP; also	most effective agent for induction of remission in acute myelocytic leukemia; also used for induction of remission acute lymphoblastic leukemia, non-Hodgkin's lymphomas; usually used in combination chemotherapy	Orally effective	bone marrow depression,

6. Drug Resistance

One of the fundamental issue in cancer chemotherapy is the development of cellular drug resistance. It means, tumor cells are no longer respond to chemotherapeutic agents. For example, melanoma, renal cell cancer, brain cancer often become resistant to chemo.

A few known reasons:

1.Mutation in p53 tumor suppressor gene occurs in 50% of all tumors. This leads to resistance to radiation therapy and wide range of chemotherapy.

2.Defects or loss in mismatch repair (MMR) enzyme family. E.g., colon cancer no longer respond to fluoropyrimidines, the thiopurines, and cisplatins.

3.Increased expression of multidrug resistance MDR1 gene which encodes P-glycoprotein resulting in [illegible] intracellular accumulation. Drugs such as athracyclines, vinca [illegible] taxanes, campothecins, even antibody such as imatinib.