# Antibiotics (antitumor)

The antitumor antibiotics owe their cytotoxic action primarily to their **interactions with DNA, leading to disruption of DNA function**.

In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect.

They are cell cycle nonspecific, with *bleomycin* as an exception.

## A. Anthracyclines: Doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone

Doxorubicin and daunorubicin are classified as anthracycline antibiotics. Doxorubicin is the hydroxylated analog of daunorubicin.

Idarubicin, the 4 demethoxy analog of daunorubicin, epirubicin, and mitoxantrone are also available.

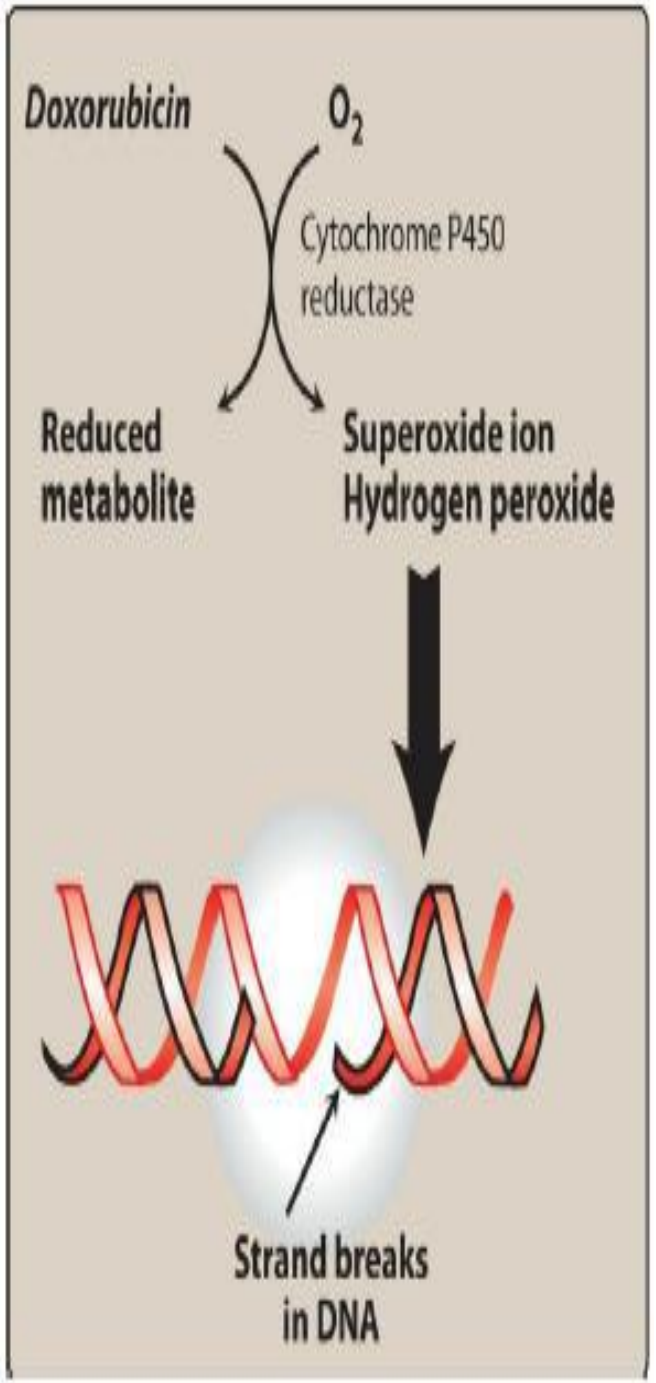
Therapeutic uses for these agents differ despite their structural similarity and apparently similar mechanisms of action.

**Doxorubicin used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast cancer, as well as for treatment of acute lymphocytic leukemia and lymphomas**.

Daunorubicin and idarubicin are used in the treatment of acute leukemias, and mitoxantrone is used in prostate cancer.

# Mechanism of action

Doxorubicin and other anthracyclines induce cytotoxicity through several different mechanisms. For example, **doxorubicin derived free radicals can induce membrane lipid peroxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines.**




# Pharmacokinetics

**These agents must be administered intravenously, because they are inactivated in the GI tract.**

Extravasation is a serious problem that can lead to **tissue necrosis.** The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed.

They **do not** penetrate the blood brain barrier or the testes. These agents undergo extensive hepatic metabolism, and dosage adjustments are needed in patients with impaired hepatic function.

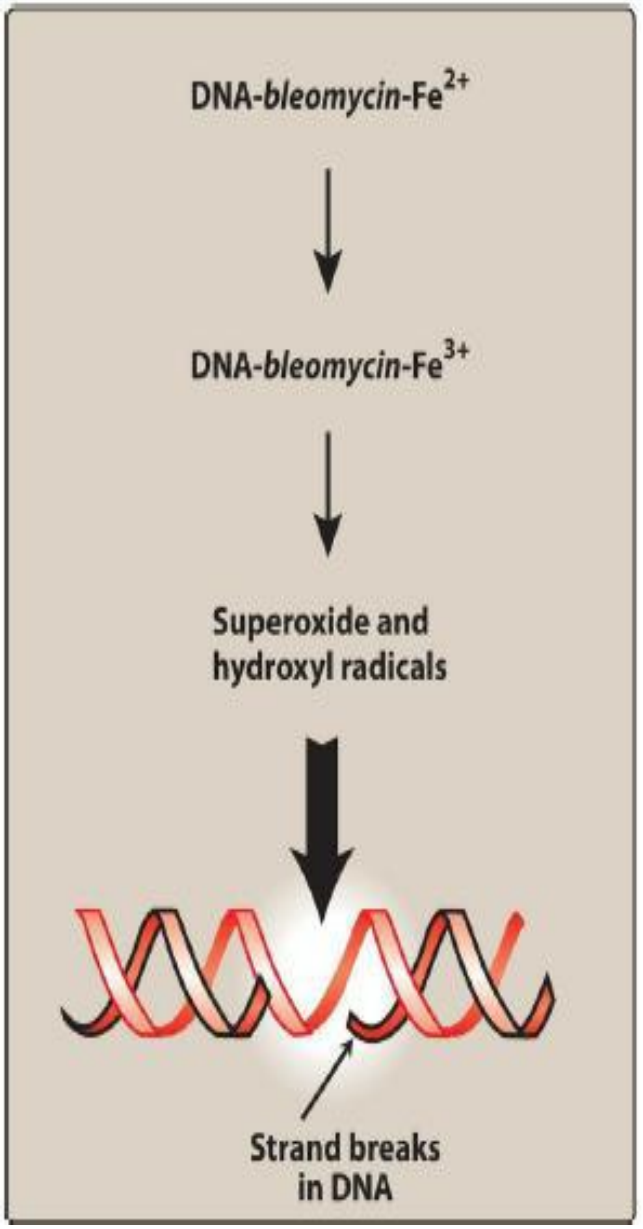
Biliary excretion is the major route of elimination. . Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and red discoloration of urine may occur.

# Adverse effects

**Irreversible, dose dependent cardiotoxicity is the most serious adverse reaction and is more common with daunorubicin and doxorubicin than with idarubicin and epirubicin.**

There has been some success with the iron chelator dexrazoxane in protecting against the cardiotoxicity of doxorubicin.

The liposomal encapsulated doxorubicin is reported to be **less** cardiotoxic than the standard formulation.




**B. Bleomycin:** Bleomycin is a mixture of different copper chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process.

Bleomycin is cell cycle specific and causes cells to accumulate in the G2 phase. It is primarily used in the treatment of testicular cancers and Hodgkin lymphoma.

**Mechanism of action**

A DNA bleomycin Fe2+ complex appears to undergo oxidation to bleomycin Fe3+. The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting istrand breakage and chromosomal aberrations.

## Pharmacokinetics

Bleomycin is administered by a number of routes. The bleomycin--inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in the lung and absent in the skin, accounting for toxicity in those tissues. Most of the parent drug is excreted unchanged in the urine, necessitating dose adjustment in patients with renal failure.

## Adverse effects

**Pulmonary toxicity is the most serious adverse effect, progressing from rales,** cough, and infiltrate to potentially fatal fibrosis.

The pulmonary fibrosis that is caused by bleomycin is often referred as "***bleomycin lung***."

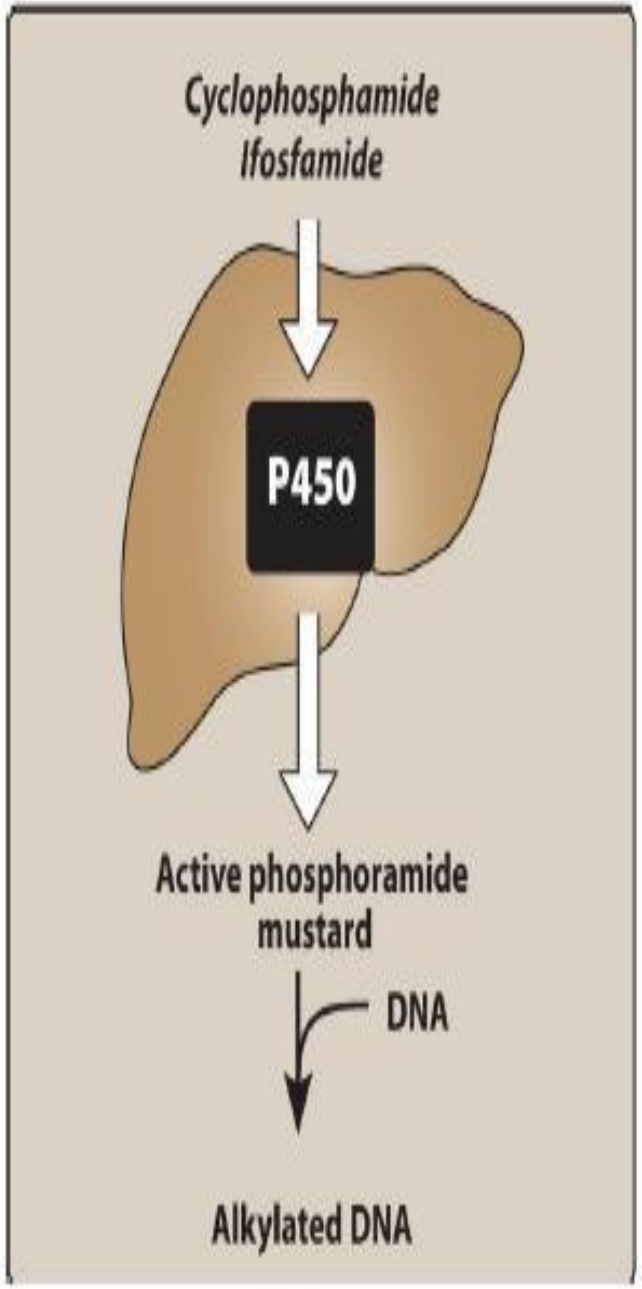
Hypertrophic skin changes and hyperpigmentation of the hands are prevalent. Bleomycin is unusual in that myelosuppression is rare.

# Alkylating Agents

Alkylating agents exert their **cytotoxic** effects by **covalently binding to nucleophilic groups on various cell constituents.**

Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, even though they are **most** toxic for rapidly dividing cells.

They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, **all** are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.




## A. Cyclophosphamide and ifosfamide

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. These agents have a broad clinical spectrum and are used as **single agents or in combinations** in the treatment of a wide variety of neoplastic diseases, such as non-Hodgkin lymphoma, sarcoma, and breast cancer.

# Mechanism of action

Cyclophosphamide is the most commonly used alkylating agent. Both cyclophosphamide and ifosfamide are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system.

The hydroxylated intermediates then undergo metabolism to form the active compounds, phosphoramide mustard and acrolein.

Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.

## *Pharmacokinetics*

Cyclophosphamide is available in oral and IV preparations, whereas ifosfamide is IV only. Cyclophosphamide is metabolized in the liver to active and inactive metabolites, and minimal amounts are excreted in the urine as unchanged drug. Ifosfamide is metabolized primarily by CYP450 3A4 and 2B6 isoenzymes. It is mainly renally excreted.

## *Adverse effects :*

A unique toxicity of both drugs is **hemorrhagic cystitis**, which can lead to fibrosis of the bladder. Bladder toxicity has been attributed to **acrolein** in the urine in the case of cyclophosphamide and to toxic metabolites of ifosfamide.

Adequate hydration as well as IV injection of **mesna (sodium 2-mercaptoethane sulfonate),** which neutralizes the toxic metabolites, can minimize this problem.

Neurotoxicity has been reported in patients on high--dose ifosfamide, probably due to the metabolite, chloroacetaldehyde.

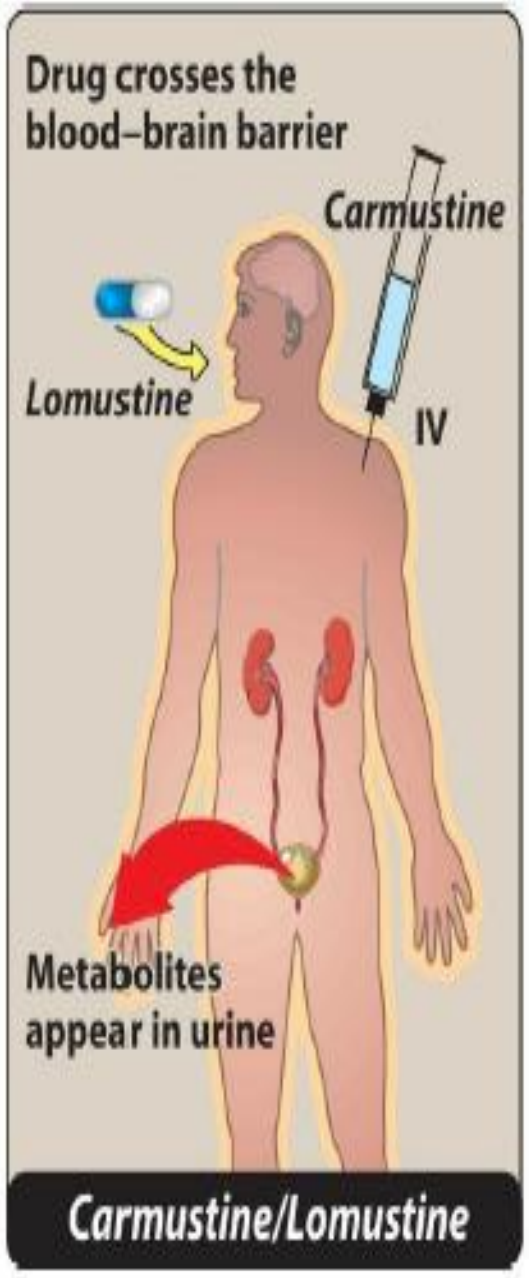
# B. Nitrosoureas

Carmustine and lomustine are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors.

## Mechanism of action

The nitrosoureas exert cytotoxic effects by an **alkylation that inhibits replication and, eventually, RNA and protein synthesis.**

Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily in cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells.




# Pharmacokinetics

Carmustine is administered IV and as chemotherapy wafer implants, whereas lomustine is given **orally**.

Because of their lipophilicity, these agents distribute widely in the body and readily penetrate the CNS. The drugs undergo extensive metabolism. Lomustine is metabolized to active products. The kidney is the major excretory route for the nitrosoureas.

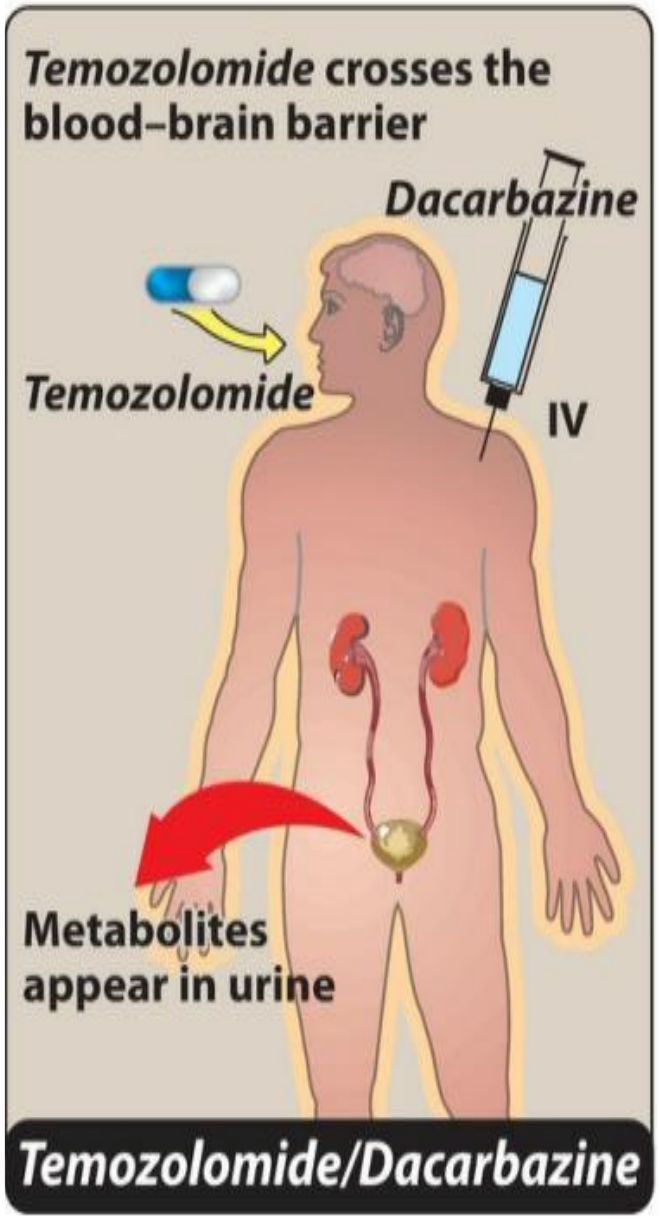
# C. Dacarbazine and temozolomide

Dacarbazine is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). The metabolite is responsible for the alkylating activity of this agent by forming methyl carbonium ions that attack the nucleophilic groups in the DNA molecule.

The cytotoxic action of dacarbazine has been attributed to the ability of its metabolite to methylate DNA on the O 6 position of guanine. Dacarbazine has found use in the treatment of melanoma and Hodgkin lymphoma.

Temozolomide is related to dacarbazine, because both must undergo biotransformation to an active metabolite, MTIC, which is likely responsible for the methylation of DNA on the O 6 and N 7 position of guanine.

Unlike dacarbazine, temozolomide does not require the CYP450 system for metabolic transformation, and it undergoes chemical transformation at normal physiological pH. Temozolomide also inhibits the repair enzyme, O-6-guanine--DNA alkyltransferase.




Temozolomide differs from dacarbazine in that it crosses the blood brain barrier and, therefore, is used in the treatment of brain tumors such as glioblastomas and astrocytomas. It is also used in metastatic melanoma.

Temozolomide is administered **intravenously or orally** and has excellent bioavailability after oral administration. The parent drug and metabolites are excreted in urine.

# D. Other alkylating agents

**Mechlorethamine** was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in **lymphatic** cancers.

**Melphalan**, a phenylalanine derivative of nitrogen mustard, is used in the treatment of **multiple myeloma**.

This is a bifunctional alkylating agent that can be given orally, although the plasma concentration differs from patient to patient due to variation in intestinal absorption and metabolism. The dose of melphalan is carefully adjusted by monitoring the platelet and white blood cell counts.

**Chlorambucil** is another bifunctional alkylating agent that is used in the treatment of chronic lymphocytic leukemia.

**Busulfan** is an alkylating agent that is effective against chronic myelogenous leukemia. This agent can cause pulmonary fibrosis ("busulfan lung"). Like other alkylating agents, all of these agents are leukemogenic.

# Microtubule Inhibitors

## A. Vincristine and vinblastine

Vincristine (VX) and vinblastine (VBL) are structurally related compounds derived from the periwinkle plant, Vinca rosea. They are, therefore, referred to as the Vinca alkaloids. A less neurotoxic agent is vinorelbine (VRB). Although the Vinca alkaloids are structurally similar, their therapeutic indications are different. They are generally administered in combination with other drugs.

VX is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft tissue sarcoma, and Hodgkin and non Hodgkin lymphomas, as well as some other rapidly proliferating neoplasms.

VBL is administered with **bleomycin and cisplatin for the treatment of metastatic testicular carcinoma.** It is also used in the treatment of systemic **Hodgkin and non-Hodgkin lymphomas**.

VRB is beneficial in the treatment of advanced non–small cell lung cancer, either as a single agent or with cisplatin.

# Mechanism of action:

These agents are cell cycle specific and phase specific, because they block mitosis in metaphase (M phase).

Their binding to the microtubular protein, tubulin, blocks the ability of tubulin to polymerize to form microtubules.

Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation.

## *Pharmacokinetics*

IV injection of these agents leads to rapid cytotoxic effects and cell destruction. This, in turn, can cause hyperuricemia due to the oxidation of purines that are released from fragmenting DNA molecules. The Vinca alkaloids are concentrated and metabolized in the liver by the CYP450 pathway and eliminated in bile and feces. Dosage adjustment is required in patients with impaired hepatic function or biliary obstruction.

## Adverse effects:

VX and VBL are both associated with phlebitis or cellulitis if extravasation occurs during injection, as well as nausea, vomiting, diarrhea, and alopecia.

VBL is a potent myelosuppressant, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) and constipation are more common with VX. These agents should not be administered intrathecally. This potential **drug error can result in death**, and special precautions should be in place for administration.

## B- Paclitaxel and docetaxel

Paclitaxel was the first member of the taxane family to be used in cancer chemotherapy. Substitution of a side chain resulted in docetaxel, which is the **more potent** of the two drugs. Paclitaxel has good activity against advanced ovarian cancer and metastatic breast cancer, as well as non–small cell lung cancer when administered with cisplatin. **Docetaxel is commonly used in prostate, breast, GI, and non–small cell lung cancers.**

## Mechanism of action

Both drugs are active in the G2/M phase of the cell cycle, but unlike the Vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly, leading to the accumulation of microtubules. The microtubules formed are overly stable and nonfunctional, and chromosome desegregation does not occur. This results in cell death.

## Pharmacokinetics

These agents undergo hepatic metabolism by the CYP450 system and are excreted via the biliary system. Dosages should be reduced in patients with hepatic dysfunction.

## Adverse effects:

The dose-limiting toxicities of paclitaxel and docetaxel are neutropenia and leukopenia. Peripheral neuropathy is also a common adverse effect with the taxanes.

[**Note:** Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), patients who are treated with paclitaxel should be premedicated with dexamethasone and diphenhydramine, as well as with an H2 receptor antagonist.]

# Anticancer Drugs

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# Principles of Cancer Chemotherapy

Cancer chemotherapy aims to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest tumor progression.

The attack is generally directed toward DNA or against metabolic sites essential to cell replication.

Ideally, these anticancer drugs should interfere only with cellular processes that are **unique** to malignant cells.

Indeed, most anticancer drugs **do not** specifically recognize neoplastic cells and affect **all** kinds of proliferating cells including the normal cells.

Therefore, almost all antitumor agents have a steep dose response curve for both therapeutic and toxic effects.

Newer agents are being developed that take a different approach to cancer treatment by blocking checkpoints and allowing the patient's own immune system to attack cancer cells.

Chemotherapeutic agents also used in non cancer diseases, e.g. methotrexate in rheumatoid arthritis and psoriasis, azathioprine in organ transplantation, and hydroxyurea in sickle cell anemia.

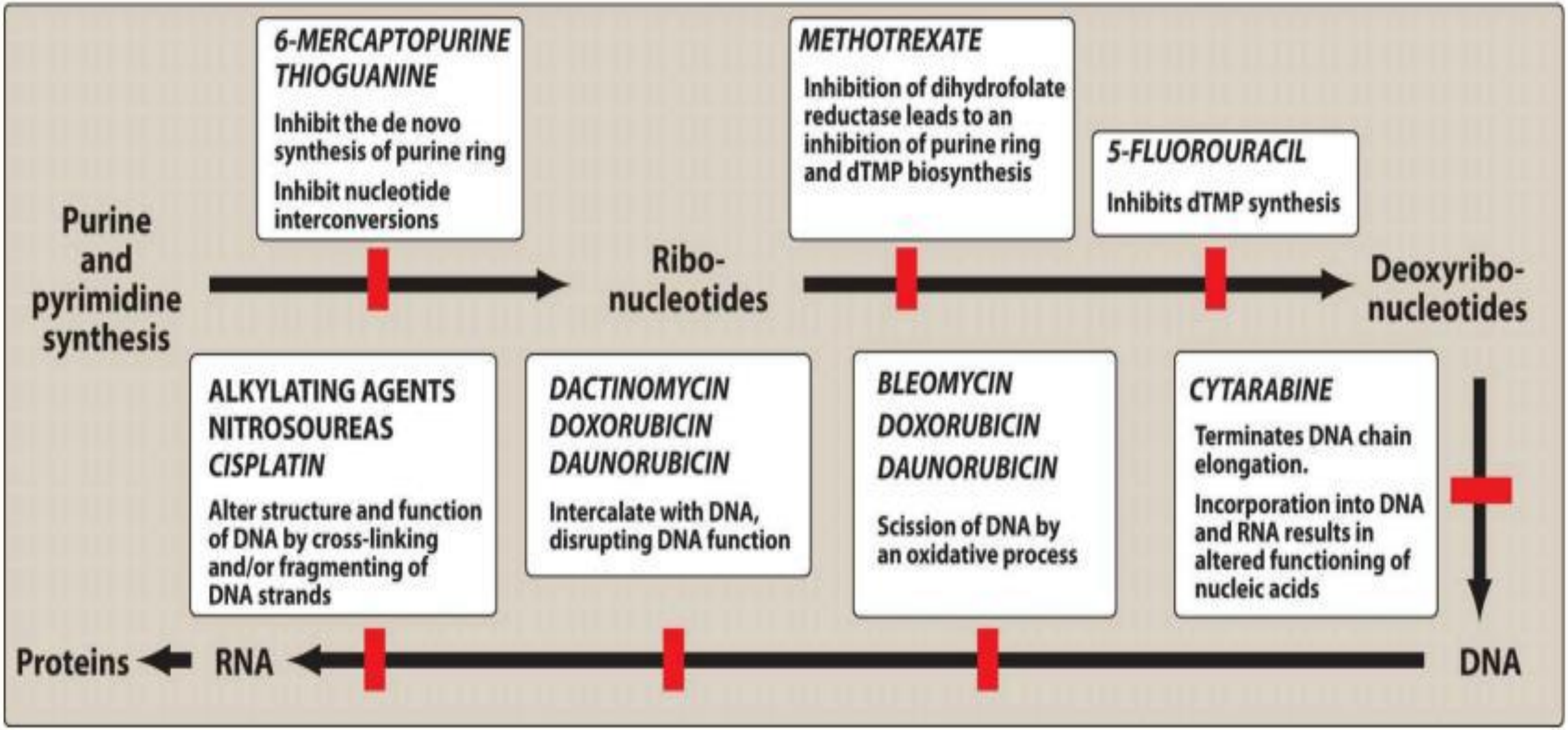
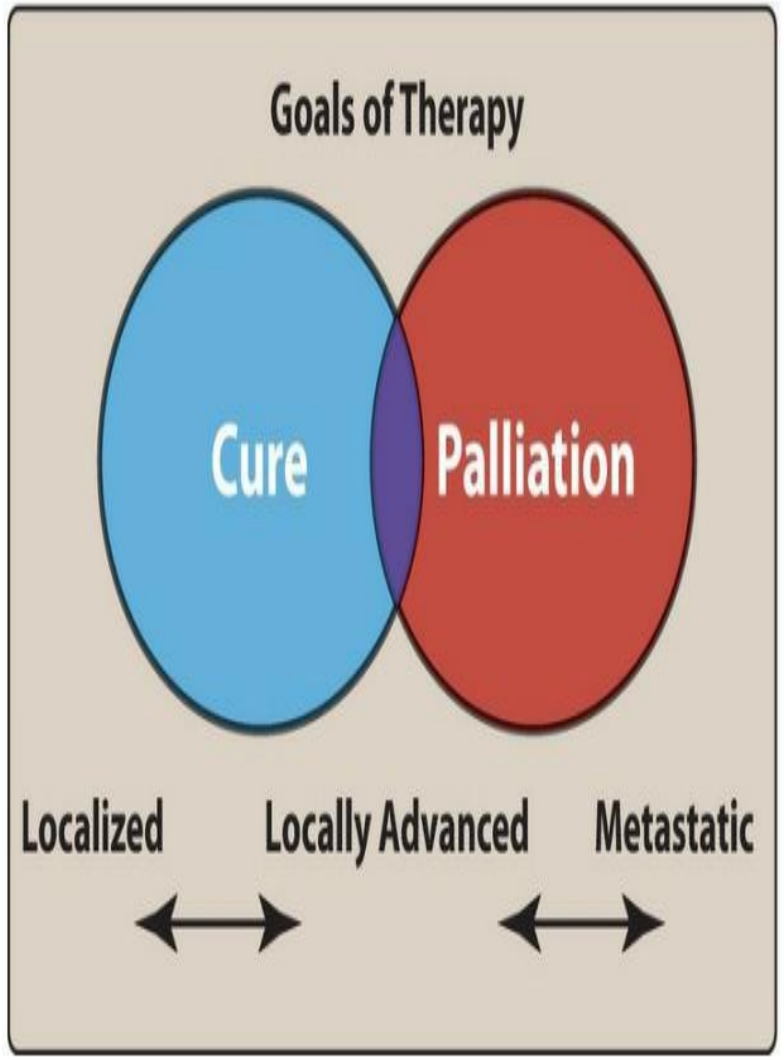



**Figure. Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.**



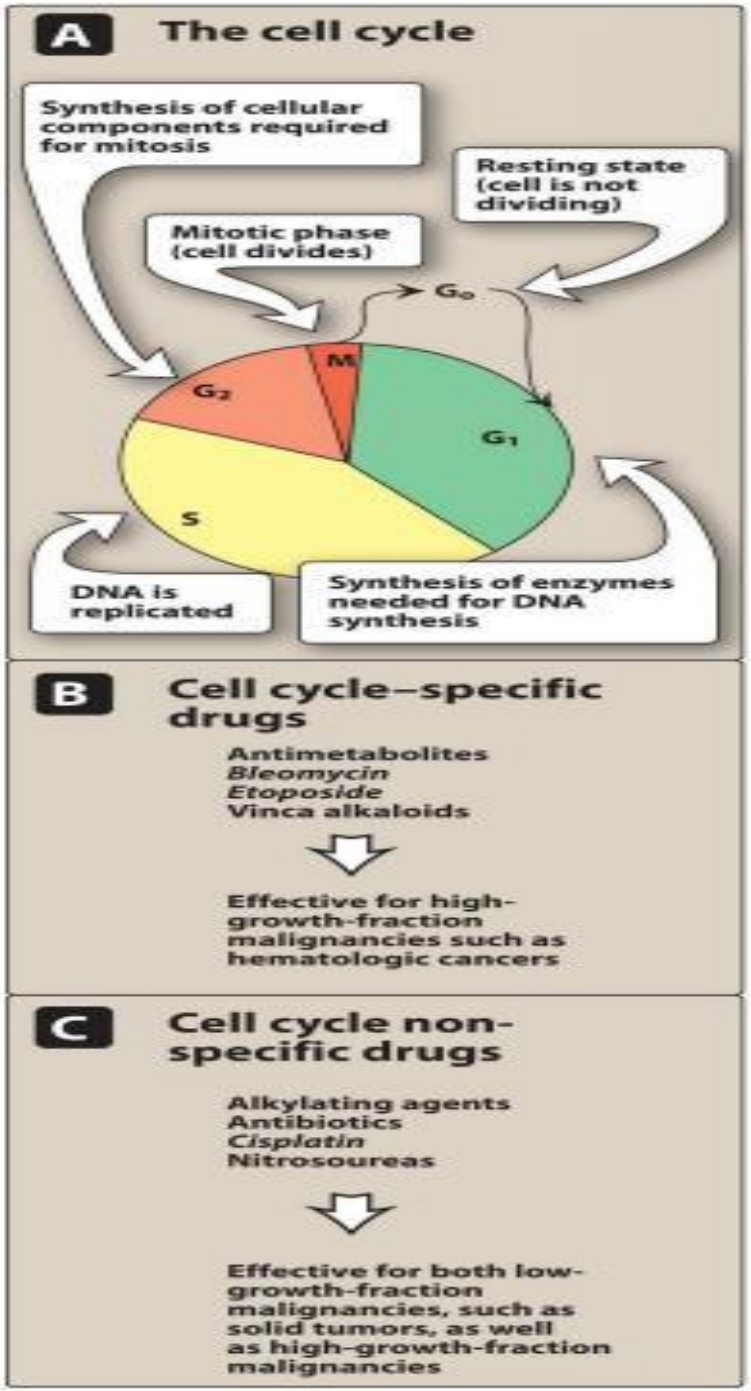

## Treatment strategies

**Goals of treatment:** Chemotherapy reduces neoplastic cell burden to maintain "normal" existence of the disease with the patient as a chronic disease, accordingly three goals intended depending upon complicated factors mainly the type and stage of cancer:

**First** fundamental goal of cancer chemotherapy is to cure the disease. Cure means long term disease free survival. True cure requires the eradication of every neoplastic cell.

**Second** goal becomes control of the disease by stopping the cancer from enlarging and spreading to extend survival and maintain the "best quality" of life.
In advanced stages of cancer, controlling the disease **is not possible**.

**Third** goal is palliation. Palliation means alleviation of symptoms and avoidance of life threatening toxicity. This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not extend survival. The goal of treatment should always be kept in mind, as it often influences treatment decisions.




# Indications for treatment:

Chemotherapy is indicated in the following cases:

a) Initial chemotherapy: indicated when the neoplasm is disseminated and are not suitable to surgery, e.g. esophageal, head and neck cancers, and leukemia.

b) Adjuvant chemotherapy: is indicated as supplemental treatment to attack micro metastases following surgery or radiation, e.g. in breast and colorectal cancers.

c) Neo adjuvant chemotherapy: given prior to surgery in an attempt to shrink the cancer in solid tumors.

d) Maintenance chemotherapy: given in low doses to cancer patients to assist in prolonging remission.

# Treatment regimens and scheduling

Drug dosages are usually calculated on the basis of **body surface area**, in an effort to tailor the dosage to each patient.

Destruction of cancer cells by chemotherapeutic agents follows **first order** kinetics (that is, a given dose of drug destroys a constant fraction of cells).

Combination chemotherapy is **more successful** than single drug treatment in most cancers for which chemotherapy is effective.

Cytotoxic agents with different toxicities, and with different molecular sites and mechanisms of action, are usually combined **at full doses.**

This results in higher response rates, due to additive and/or potentiated cytotoxic effects, and nonoverlapping host toxicities.

In contrast, agents with similar dose--limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each.

The advantages of combination chemotherapy are that it

1) Provides maximal cell killing within the range of tolerated toxicity,
2) Is effective against a broader range of cell lines in the heterogeneous tumor population, and
3) may delay or prevent the development of resistant cell lines.

**Treatment protocols:** Many cancer treatment protocols have been developed, and each is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called **RCHOP**, used for the treatment of **non Hodgkin lymphoma**, consists of **rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone**.
Therapy is scheduled intermittently to allow recovery or rescue of the immune system, which is also affected by the chemotherapeutic agents, thus reducing the risk of serious infection.

**Resistance and toxicity with chemotherapy**

**Resistance** one of the major difficulties in cancer therapy is the development of resistance to cancer chemotherapy. Resistance could be categorized into two forms:

1 **Inherited** or primary resistance: were some types of neoplasms are inherently resistant to some anticancer drug (e.g. melanoma) even when the chemotherapy treatment used for the first time.

2-- **Acquired** resistance: were the tumor cells that previously sensitive will develop resistance during treatment with chemotherapy. This type of resistance developed by modulations made by the tumor cells to overcome the lethal effect of the drug.

including **decreased** accumulation of drug (e.g. P--glycoprotein),
**insufficient** activation of the drug (e.g. 5-- FU, mercaptopurine),
**decreased** taking up the drug (e.g. methotrexate),
**increased** the concentration of target enzyme (e.g. methotrexate),
**utilization** of alternative metabolic pathway (e.g. antimetabolites),
**increased** repair of drug--induced lesions (e.g. alkylating agents),
and **mutations** in various genes that giving rise to resistant target site (e.g. overexpression of antiapoptotic genes).

Resistance to chemotherapy commonly developed with:

* Long--term, continuous,
* Suboptimal doses and
* Single drug regimens.

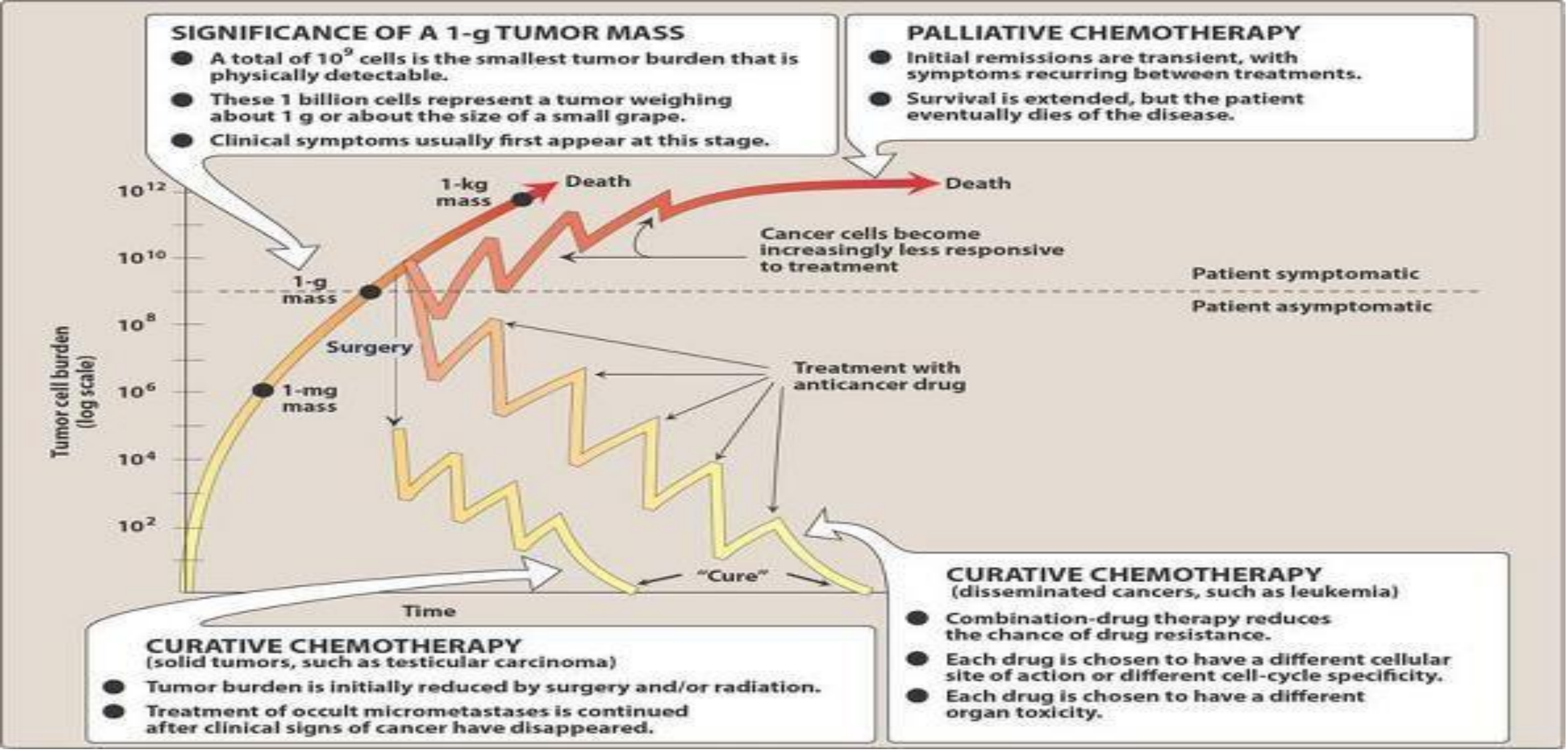
Therefore, to minimize resistance, it is advised to **use short--term, intermittent, and intensive and drug combination regimens.**

# Toxicity

Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the buccal mucosa, bone marrow, gastrointestinal [GI] mucosa, and hair follicles), contributing to the toxic manifestations of chemotherapy.

# Common adverse effects

Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to varying extents during therapy with most antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents, whereas other **adverse reactions are confined to specific agents, such as bladder toxicity with cyclophosphamide, cardiotoxicity with doxorubicin, and pulmonary fibrosis with bleomycin.**
The duration of the adverse effects varies widely. For example, alopecia is **transient**, but the cardiac, pulmonary, and bladder toxicities can be **irreversible**.

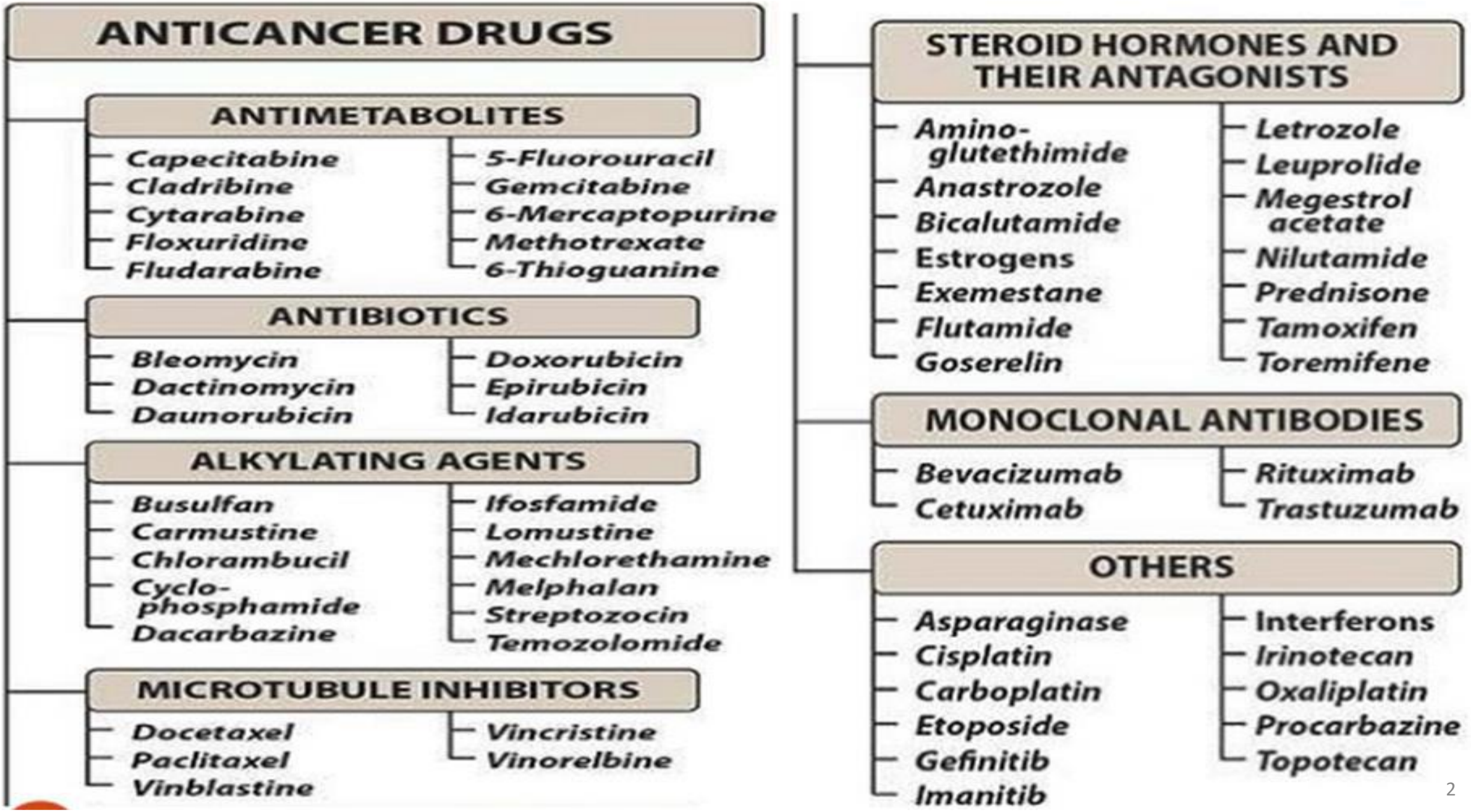



# Cancer cell burden with/without treatment

# Antimetabolites

Ass. Lec. Rabei Abdullah Salih

# 13.ANTI CANCER DRUG CLASSIFICATION



# Antimetabolites

Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by **inhibiting their synthesis or by competing with them in DNA or RNA synthesis.**

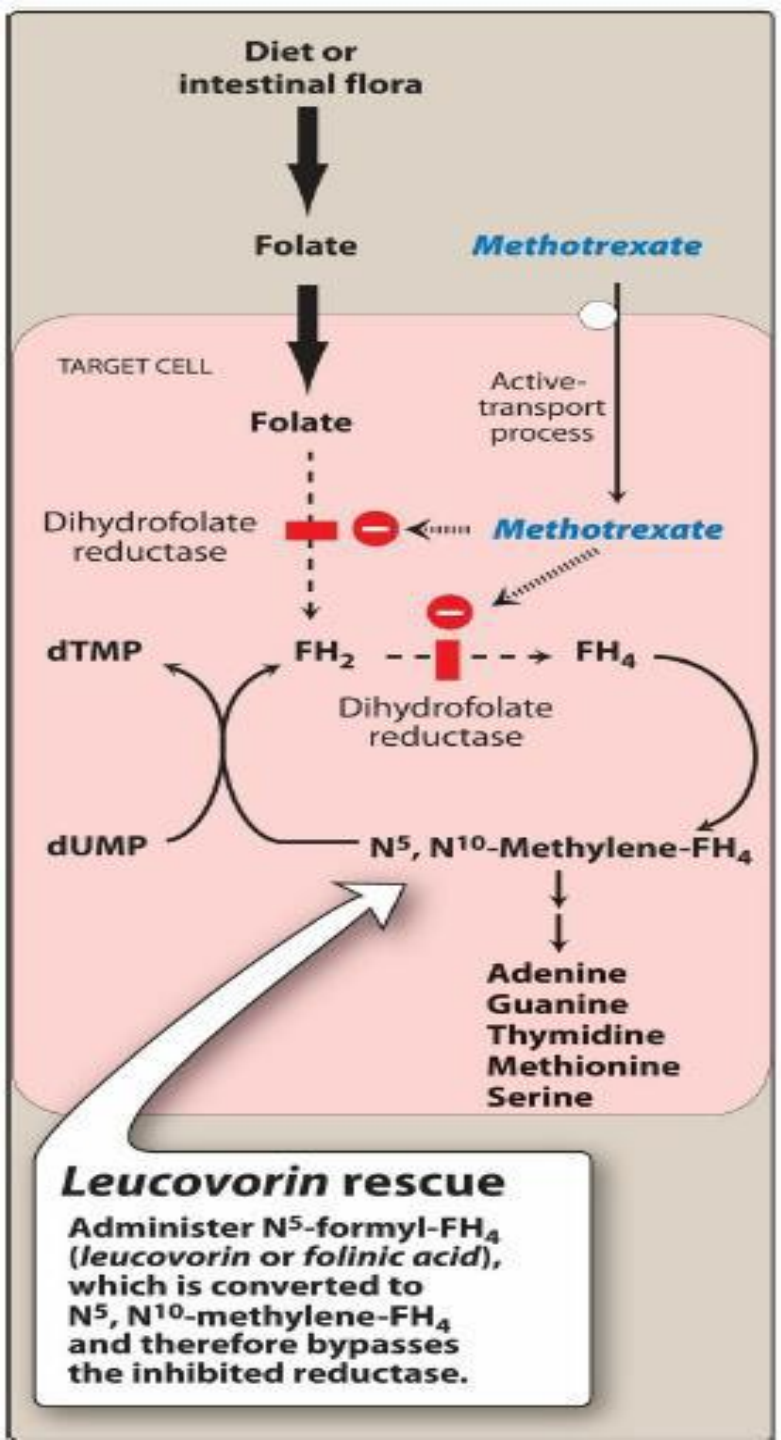
Their maximal cytotoxic effects are in S phase and are, therefore, cell cycle specific.

# Methotrexate, pemetrexed, and pralatrexate

The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one carbon units and is essential for cell replication.

Folic acid is obtained mainly from dietary sources and from that produced by intestinal flora.

Methotrexate, pemetrexed, and pralatrexate are antifolate agents.




**MTX** is structurally related to folic acid and acts as an antagonist of the vitamin by inhibiting mammalian dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4). The inhibition of DHFR can only be reversed by a 1000 fold excess of the natural substrate, dihydrofolate (FH2), or by administration of leucovorin, which bypasses the blocked enzyme and replenishes the folate pool.

Folinic acid (leucovorin) could restore MTX inhibition by replenishing THF pool as it bypasses the MTX inhibition sites.

**Pemetrexed** is an antimetabolite similar in mechanism to methotrexate. However, in addition to inhibiting DHFR, it also inhibits thymidylate synthase and other enzymes involved in folate metabolism and DNA synthesis.

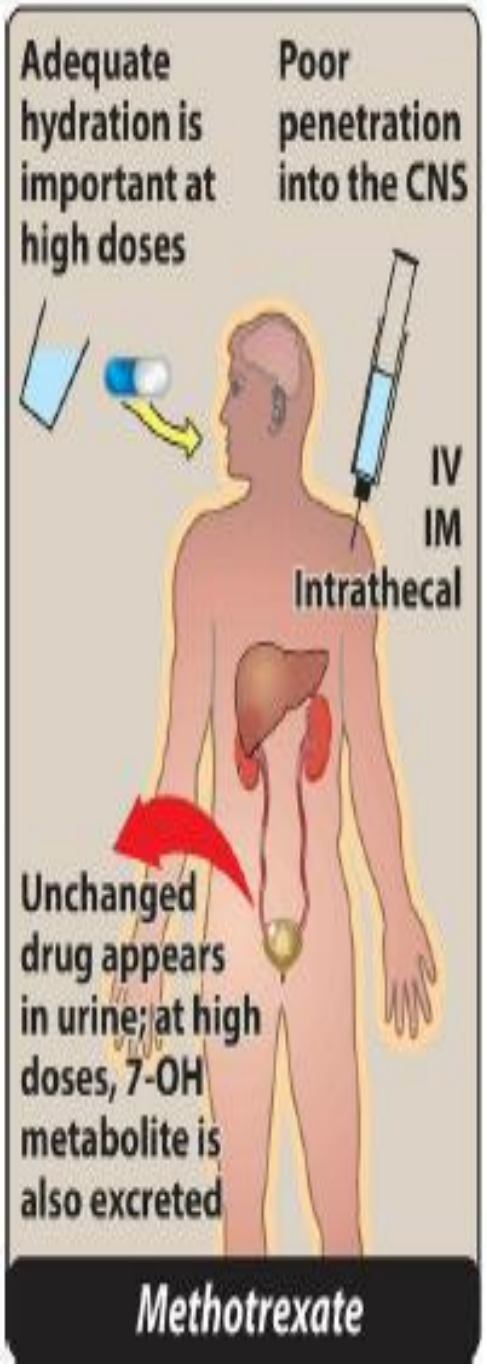
**Pralatrexate** is an antimetabolite that also inhibits DHFR.

# ***Therapeutic uses***

MTX, usually in **combination** with other drugs, is effective against acute lymphocytic leukemia, Burkitt lymphoma in children, breast cancer, bladder cancer, and head and neck carcinomas.

In addition, low dose MTX is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis, as well as Crohn disease.

Pemetrexed is primarily used in non–small cell lung cancer. Pralatrexate is used in **relapsed or refractory T-cell lymphoma.**




# *Pharmacokinetics*

MTX is variably absorbed orally at low doses from the GI tract, it can also be administered by intramuscular, intravenous (IV), and intrathecal routes.

Small amounts of MTX undergo hydroxylation at the 7th position to form 7 hydroxymethotrexate.

**This derivative is less water soluble than MTX and may lead to crystalluria.**

Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity.

Excretion of the parent drug and the 7 OH metabolite occurs primarily via urine.

# *Adverse effects:*

MTX, Pemetrexed and pralatrexate should be given with folic acid and vitamin B12 supplements to reduce hematologic and GI toxicities.

Pretreatment with corticosteroids to prevent cutaneous reactions is recommended with pemetrexed.

However, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits, CNS disturbances, GI upset, and skin discoloration and eruptions.

# Purine analogs

Drugs belong to this category are guanine analogs (6 mercaptopurine, 6 thioguanine), and adenosine analogs (fludarabine, and cladribine).

Some drugs in this category dose **not used** in cancer chemotherapy but as immunosuppressant (e.g. azathioprine), antiviral (e.g. acyclovir, zidovudine) and hypouricemic agent (allopurinol).

# *6 Mercaptopurine*

6 Mercaptopurine (6 MP), a purine antimetabolite, is the thiol analog of hypoxanthine.

6 MP and 6 thioguanine were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: Azathioprine, an immunosuppressant, exerts its cytotoxic effects after conversion to 6 MP.]

6 MP is used principally in the maintenance of remission in acute lymphoblastic leukemia.

6 MP and its analog, azathioprine, are also beneficial in the treatment of Crohn's disease.

# *Adenosine analogs*

## Fludarabine and Cladribine.

Both agents are adenosine analogs used in leukemia's and lymphomas. Fludarabine is the phosphate of 2 fluoroadenine arabinoside, a purine nucleotide analog.

It is useful in the treatment of chronic lymphocytic leukemia, hairy cell leukemia, and indolent non Hodgkin lymphoma.

Fludarabine is a prodrug, and the phosphate is removed in the plasma to form 2-F-ara-A, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase).

Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA.

This decreases their synthesis in the S phase and affects their function.

Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase, as well as other mechanisms.

Fludarabine is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoroadenine.

# Pyrimidine analogs

This category of chemotherapeutic agents designed as a false metabolite to inhibit pyrimidine nucleotide synthesis, thus inhibit DNA synthesis, and to lesser extent inhibit RNA synthesis. Pyrimidine analogs could be divided into two groups according to the nucleotide target: thymidine and cytosine inhibitors.

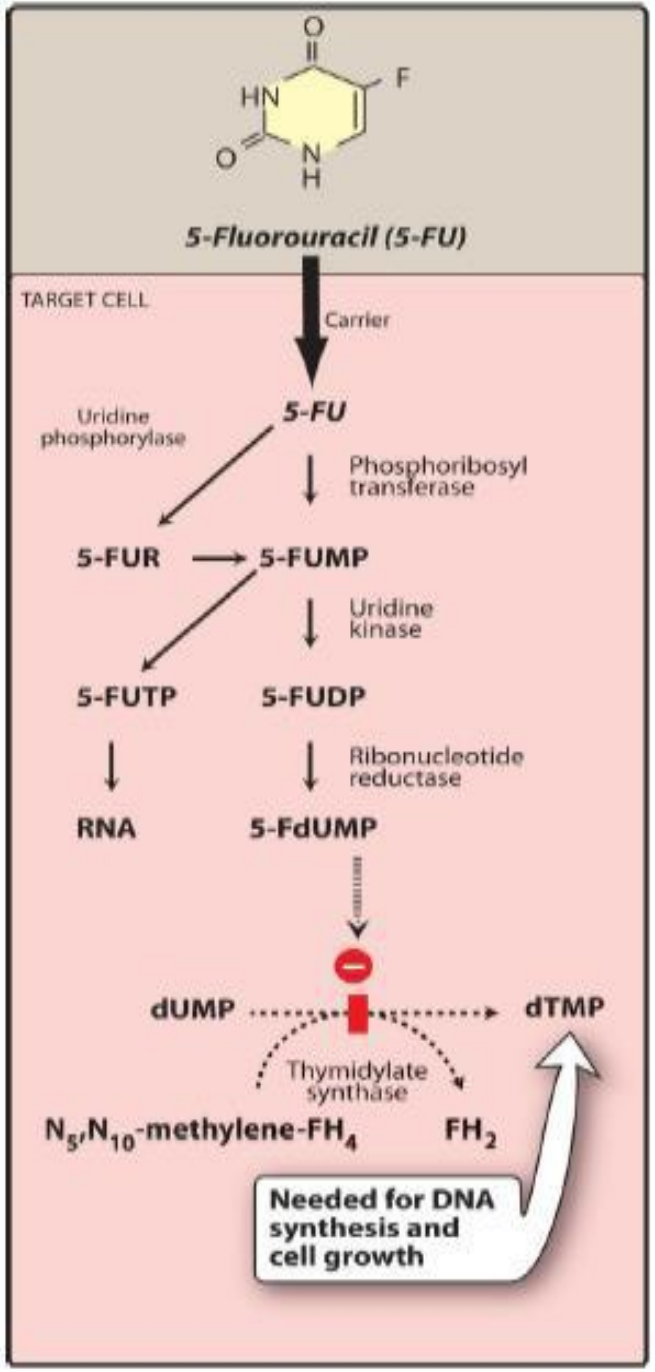
Thymidine inhibitors include 5 fluorouracil (5 FU), capecitabine; while the cytosine inhibitors include cytarabine, 5 azacytidine and gemcitabine.

# 1-( 5 Fluorouracil)

5 Fluorouracil (5 FU), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis.

5 FU is employed primarily in the treatment of slow growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas).

When applied topically, 5 FU is also effective for the treatment of superficial basal cell carcinomas.




**Mechanism of action :**

5 FU itself is **devoid** of antineoplastic activity. It enters the cell through a carrier mediated transport system and is converted to the corresponding deoxynucleotide (5 fluorodeoxyuridine monophosphate [**5 FdUMP**]), which competes with deoxyuridine monophosphate for thymidylate synthase, thus inhibiting its action.

DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and "thymidine less death" of rapidly dividing cells.

[Note: Leucovorin is administered with 5 FU, because the reduced folate coenzyme is required in the thymidylate synthase inhibition].

5 FU is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the 5 FU, damaging the DNA. 5 FU produces the anticancer effect in the S phase of the cell cycle.

# Pharmacokinetics

Because of severe toxicity to the GI tract, 5 FU is administered IV or, in the case of skin cancer, topically. The drug penetrates well into all tissues, including the CNS.

5 FU is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro β alanine, which is removed in the urine. Elevated levels of dihydropyrimidine dehydrogenase (DPD) can increase the rate of 5 FU catabolism and decrease its bioavailability.

Patients with DPD deficiency may experience severe toxicity manifested by **pancytopenia, mucositis, and life threatening diarrhea**. Knowledge of DPD activity in an individual should allow more appropriate dosing of 5 FU.

## 2. Capecitabine

Capecitabine is a fluoropyrimidine carbamate. It is used in the treatment of colorectal and metastatic breast cancer. Capecitabine is well absorbed following oral administration. After being absorbed, capecitabine, which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to 5 FU.

This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors. Thus, the cytotoxic activity of capecitabine is the same as that of 5 FU and is tumor specific.

The most important enzyme inhibited by 5 FU (and, thus, capecitabine) is thymidylate synthase.

## Cytidine analogs

These pyrimidine inhibitors are cytidine analogs with antineoplastic action include cytarabine, 5 azacytidine and gemcitabine.

### 1- Cytarabine

Cytarabine : is an analog of deoxycytidine in which the natural ribose residue is replaced by D arabinose. Cytarabine acts as a pyrimidine antagonist. The major clinical use of cytarabine is in acute nonlymphocytic (myelogenous) leukemia (AML).

Cytarabine enters the cell by a carrier mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate or ara- CTP) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase.

The nucleotide is also incorporated into nuclear DNA and can terminate chain elongation. It is, therefore, S phase (and, hence, cell cycle) specific.

# Pharmacokinetics

Cytarabine is **not** effective when given orally, because of deamination to the noncytotoxic ara U by cytidine deaminase in the intestinal mucosa and liver.

Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts. Therefore, it may also be injected intrathecally. Cytarabine undergoes extensive oxidative deamination in the body to ara U, a pharmacologically inactive metabolite.

Both cytarabine and ara U are excreted in urine.

## 2 Azacitidine

Azacitidine is a pyrimidine nucleoside analog of cytidine. It is used for the treatment of myelodysplastic syndromes and AML. Azacitidine undergoes activation to the nucleotide metabolite azacitidine triphosphate and gets incorporated into RNA to inhibit RNA processing and function. It is S phase cell cycle specific.

## 3 Gemcitabine

Gemcitabine is an analog of the nucleoside deoxycytidine. It is used most commonly for pancreatic cancer and non small cell lung cancer. Gemcitabine is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2′, difluorodeoxycytidine triphosphate. Gemcitabine is administered by IV infusion. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine.

# Lec- 3
# AntiCancer

Ass. Lec. Rabei Abdullah Salih

# Steroid Hormones and Their Antagonists (antitumor)

Tumors that are sensitive to steroid hormones may be either:-

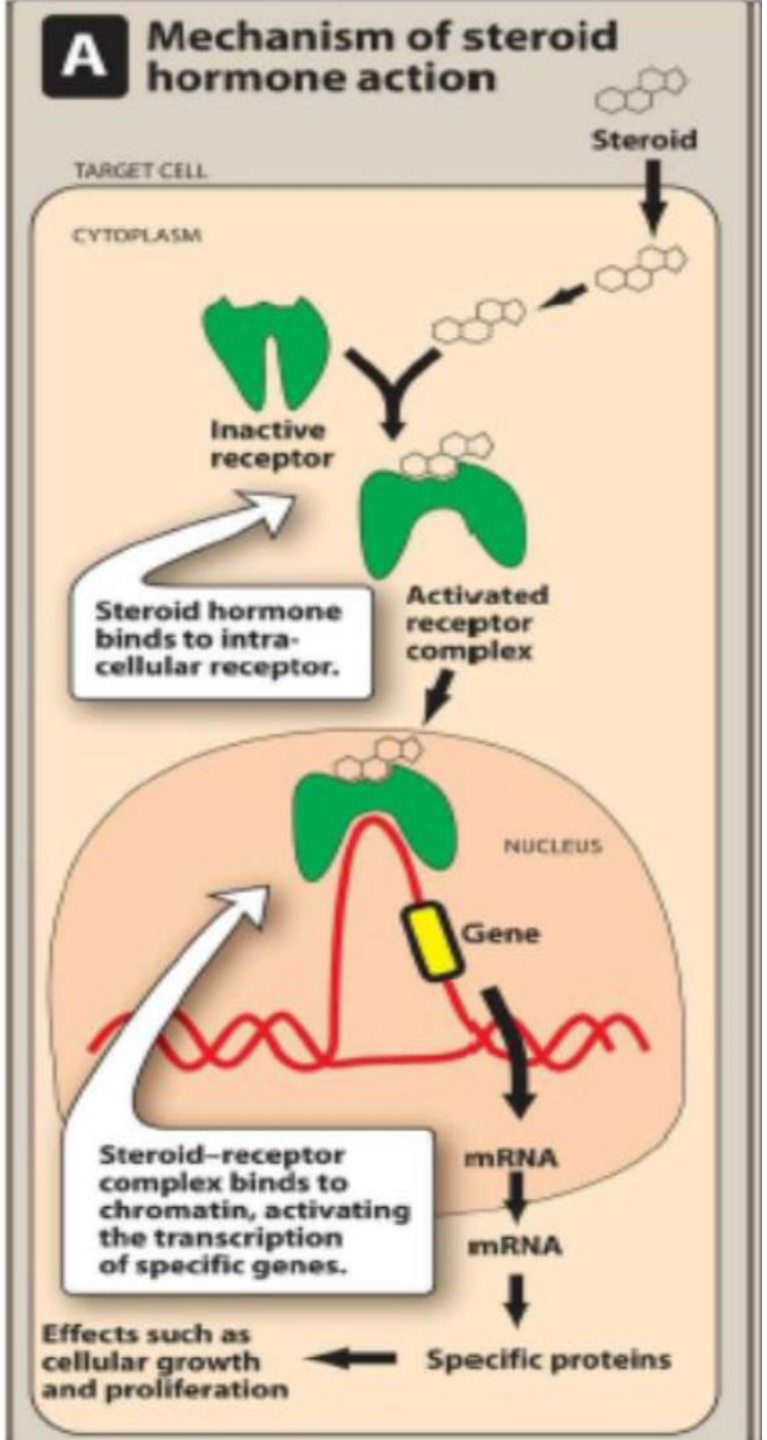
1-hormone responsive, in which the tumor regresses following treatment with a specific hormone; or

2-hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or

3- Both.

Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy (surgical removal of one or both testes for patients with advanced prostate cancer) or by drugs (for example, in breast cancer treatment with the antiestrogen tamoxifen prevents estrogen stimulation of breast cancer cells).

For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone.




# A. Tamoxifen

Tamoxifen is a selective estrogen modulator (SERM). It is an estrogen **antagonist** in breast tissue and an **agonist** in other tissues, such as bone and the endometrium.

Tamoxifen is used for first-line therapy in the treatment of estrogen receptor–positive breast cancer. It is also used for prevention of breast cancer in high-risk women.

## Mechanism of action

Tamoxifen competes with estrogen for binding to estrogen receptors in the breast tissue, and inhibits estrogen induced growth of breast cancer.

**The result is**

- **depletion (down-regulation) of estrogen receptors, and the**
- **growth-promoting effects of the natural hormone and other growth factors are suppressed.**

## Pharmacokinetics

Tamoxifen is effective after oral administration. It is partially metabolized by the liver. Some metabolites possess estrogen antagonist activity, whereas others have agonist activity. Unchanged drug and metabolites are excreted predominantly through the bile into the feces.

Tamoxifen is an inhibitor of CYP3A4 and P-glycoprotein.

## Adverse effects

Adverse effects caused by tamoxifen include : Hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (due to estrogenic activity of the drug and some of its metabolites in the endometrial tissue).

Tamoxifen has the potential to **cause endometrial cancer, thromboembolism and effects on vision**.

# B. Fulvestrant and raloxifene

Fulvestrant is an estrogen receptor antagonist that is given via IM injection to patients with **hormone receptor–positive metastatic breast cancer**.

This agent binds to and causes estrogen receptor down regulation on tumors and other targets. Raloxifene is an oral SERM that blocks estrogen effects in the uterine and breast tissues, while promoting effects in the bone to inhibit resorption.

This agent reduces the risk of estrogen receptor–positive invasive breast cancer in postmenopausal women. Both drugs are known to cause hot flashes, arthralgias, and myalgias.

## C. Aromatase inhibitors

The aromatase reaction is responsible for extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissues, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

### 1. Anastrozole and letrozole

Anastrozole and letrozole are **nonsteroidal aromatase inhibitors**. These agents are considered first-line drugs for the treatment of breast cancer in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis. Anastrozole and letrozole **do not predispose patients to endometrial cancer**. Both drugs are extensively metabolized in the liver, and metabolites and parent drug are excreted primarily in the urine.

### 2. Exemestane

A **steroidal, irreversible inhibitor of aromatase,** Exemestane, is well absorbed after oral administration and widely distributed. Hepatic metabolism occurs via the CYP3A4 isoenzyme. Because the metabolites are excreted in urine, doses of the drug must be adjusted in patients with renal failure.

Major toxicities are nausea, fatigue, and hot flashes. Alopecia and dermatitis have also been noted.

## D. Leuprolide, goserelin, and triptorelin

Gonadotropin-releasing hormone (GnRH) is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones:

1-Luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes, and

2-Follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen.

Leuprolide, goserelin, and triptorelin are synthetic analogs of GnRH. As GnRH analogs, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen synthesis are reduced. Response to leuprolide in prostatic cancer is equivalent to that of orchiectomy with regression of tumor and relief of bone pain. These drugs have some benefit **in premenopausal women with advanced breast cancer and have largely replaced estrogens in therapy for prostate cancer.**

Leuprolide is available as:

1) A **subcutaneous daily** injection,

2) A **subcutaneous depot** injection, or

3) An **intramuscular depot injection** to treat metastatic carcinoma of the prostate.

Goserelin acetate is a subcutaneous implant, and triptorelin pamoate is injected intramuscularly.

Levels of androgen in prostate cancer patients may initially rise, but then fall to castration levels.

The adverse effects of these drugs, including Impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

# E. Antiandrogens

Flutamide, nilutamide, bicalutamide, and enzalutamide are oral antiandrogens used in the treatment of **prostate cancer**.

They compete with the natural hormone for binding to the androgen receptor and prevent its action in the prostate.

Adverse effects include : gynecomastia, constipation, nausea, and abdominal pain. Rarely, liver failure has occurred with flutamide. Nilutamide can cause visual problems.

# Platinum Coordination Complexes

## A. Cisplatin, carboplatin, and oxaliplatin

Cisplatin was the first member of the platinum coordination complex class of anticancer drugs, but because of severe toxicity, carboplatin was developed.

Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. It has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with VBL and bleomycin, ovarian carcinoma in combination with cyclophosphamide, or alone for bladder carcinoma.

Carboplatin is used when patients cannot be vigorously hydrated, as is required for cisplatin treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity.

**Oxaliplatin is a closely related analog of carboplatin used in the setting of colorectal cancer.**

## Mechanism of action

**The mechanism of action of these agents is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, cisplatin persists as the neutral species, which enters the cell and loses chloride in the low-chloride milieu. It then binds to guanine in DNA, forming inter- and intrastrand cross-links. The resulting cytotoxic lesion inhibits both polymerases for DNA replication and RNA synthesis.**

Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions of these drugs in the G1 and S phases.

## Pharmacokinetics

These agents are administered via **IV infusion**. Cisplatin and carboplatin can also be given intraperitoneally for ovarian cancer and intra-arterially to perfuse other organs. The highest concentrations of the drugs are found in the liver, kidney, and intestinal, testicular, and ovarian cells, but little penetrates into the cerebrospinal fluid (CSF). The renal route is the main pathway of excretion.

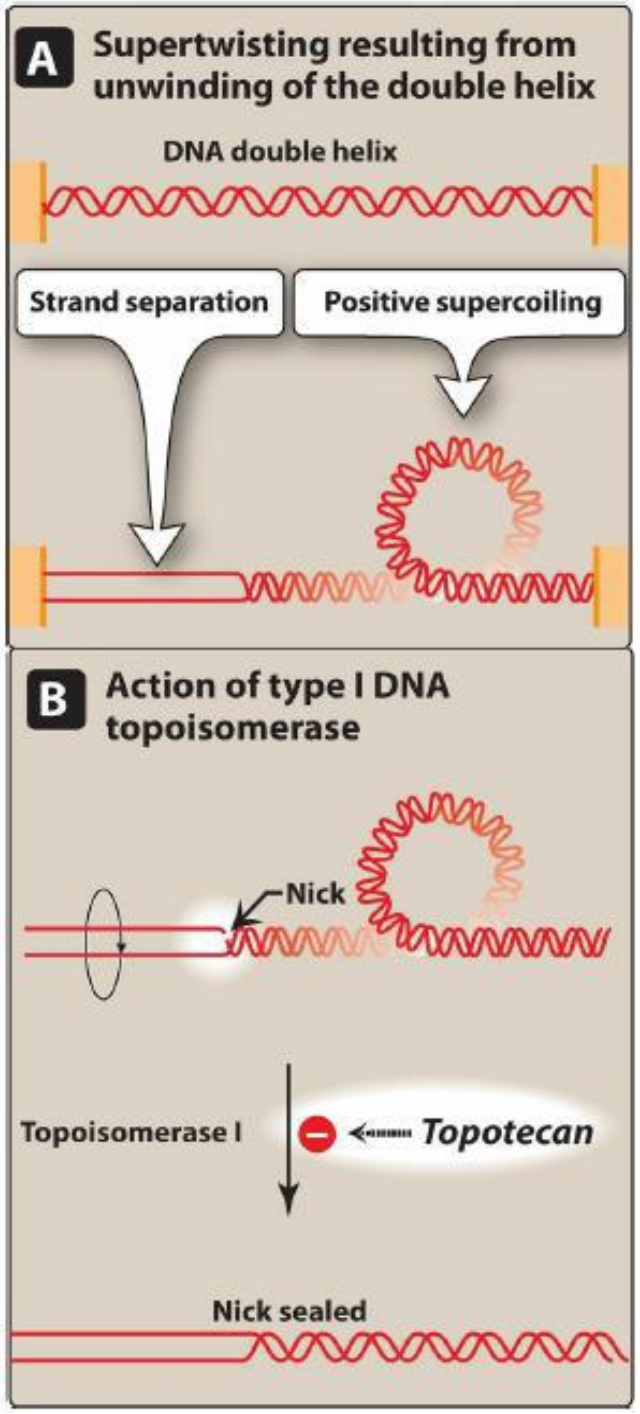
## Adverse effects

Severe nausea and vomiting occurs in most patients after administration of cisplatin and may continue for as long **as 5 days**.

Premedication with antiemetic agents is required. **The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be prevented by aggressive hydration.**

Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus. Unlike cisplatin, carboplatin causes only mild nausea and vomiting, and it is rarely nephro, neuro-, or ototoxic. The dose-limiting toxicity is myelosuppression.

**Oxaliplatin** has a distinct adverse effect of **cold induced peripheral neuropathy** that usually resolves within 72 hours of administration. It also causes myelosuppression and cumulative peripheral neuropathy. Hepatotoxicity has also been reported. These agents may cause hypersensitivity reactions ranging from skin rashes to anaphylaxis.




# Topoisomerase Inhibitors

These agents exert their mechanism of action via inhibition of topoisomerase enzymes, a class of enzymes that reduce supercoiling of DNA.

## A. Camptothecins

Camptothecins are plant alkaloids originally isolated from the Chinese tree Camptotheca.

Irinotecan and topotecan are semisynthetic derivatives of camptothecin. Topotecan is used in **metastatic ovarian cancer** when primary therapy has failed and also in the treatment **of small cell lung cancer.**

Irinotecan is used with 5-FU and leucovorin for the treatment of colorectal carcinoma.

## Mechanism of action

These drugs are S-phase specific and inhibit topoisomerase I, which is essential for the replication of DNA in human cells. SN-38 (the active metabolite of irinotecan) is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I. The topoisomerases relieve torsional strain in DNA by causing reversible, single strand breaks.

# Adverse effects:

Bone marrow suppression, particularly neutropenia, is the dose limiting toxicity for topotecan.

Frequent blood counts should be performed in patients receiving this drug. Myelosuppression is also seen with irinotecan.

Acute and delayed diarrhea with irinotecan may be severe and require treatment with atropine during the infusion or high doses of loperamide in the days following the infusion.

# B. Etoposide

Etoposide is a semisynthetic derivative of the plant alkaloid, podophyllotoxin. This agent blocks cells in the late S to G2 phase of the cell cycle, and the **major target is topoisomerase II.**

Binding of the drug to the enzyme–DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks.

Etoposide finds its major clinical use in the treatment of lung cancer and in combination with bleomycin and cisplatin for testicular carcinoma.

Etoposide may be administered either IV or orally. Dose-limiting myelosuppression (primarily ***leukopenia***) is the major toxicity.

| DRUG | MECHANISM OF ACTION | ADVERSE EFFECTS | MONITORING PARAMETERS | NOTES |
|---|---|---|---|---|
| ***Bevacizumab*** | Binds VEGF and prevents binding of VEGF to its receptors on endothelial cells<br>Inhibits vascularization of the tumor | Hypertension, GI perforation, proteinuria, wound healing problems, bleeding | BP, urine protein, signs and symptoms of bleeding | Hold for recent or upcoming surgical procedures |
| ***Cetuximab*** | Binds to EGFR and competitively inhibits the binding of epidermal growth factor and other ligands<br>Inhibits tumor cell growth and increases apoptosis | Skin rash, electrolyte wasting, infusion reaction, diarrhea | Electrolytes, vital signs during infusion | Premedication with antihistamine required before infusion; rash equated with increased response |
| ***Daratumumab*** | Binds to the transmembrane protein CD38 on multiple myeloma cells and causes cell lysis | Infusion reactions, diarrhea, fatigue, pyrexia | CBC with differential, vital signs during infusion | Can bind CD38 on red blood cells<br>Type and screen patients before starting therapy<br>Premedication with antihistamines, antipyretics, and corticosteroids required |
| ***Ramucirumab*** | Binds VEGF receptor 2 and blocks binding of VEGF receptor ligands | Proteinuria, hypertension, wound healing problems, bleeding | BP, urine protein, signs and symptoms of bleeding | Hold for recent or upcoming surgical procedures |
| ***Rituximab*** | Targets the CD20 antigen expressed on the surface of pre-B lymphocytes and mature B lymphocytes | Fatal infusion reaction, TLS, mucocutaneous reactions, PML | Vital signs during infusion, TLS labs | Fatal reactivation of hepatitis B<br>Premedication with antihistamine and acetaminophen required<br>Increased risk of nephrotoxicity when given with *cisplatin* |
| ***Trastuzumab*** | Inhibits the proliferation of human tumor cells that overexpress HER2 | Cardiomyopathy, infusion-related fever and chills, pulmonary toxicity, headache, nausea/vomiting | LVEF, CBC, pulmonary toxicity due to infusion reaction | Embryo-fetal toxicity<br>Neutropenia in combination with chemotherapy<br>Premedication with antihistamine and *acetaminophen* required |

# Monoclonal antibodies

Monoclonal antibodies are an active area of drug development for anticancer therapy and other nonneoplastic diseases, because they are directed at specific targets and often have different adverse effect profiles as compared to traditional chemotherapy agents. All of these agents are administered intravenously, and infusion-related reactions are common.

| DRUG | MECHANISM OF ACTION | ADVERSE EFFECTS | NOTABLE DRUG INTERACTIONS | MONITORING PARAMETERS | NOTES |
|---|---|---|---|---|---|
| ***Afatinib*** | Inhibits EGFR tyrosine kinase | Diarrhea, rash, stomatitis, paronychia, nausea, vomiting, pruritus | P-gp inhibitors and inducers | CBC, CMP | Administer on an empty stomach<br>Reduce dose for significant diarrhea<br>Use effective contraception for female patients |
| ***Dabrafenib*** | Inhibits mutated BRAF kinases | Pyrexia, rash, arthralgia, cough, embryo-fetal toxicity | CYP3A4 inhibitors and substrates; CYP2C8 inhibitors and substrates; substrates of CYP2C9, CYP2C19, or CYP2B6 | Glucose, symptoms of heart failure or bleeding, CBC, BMP, INR (if *warfarin*) | Use effective contraception for female patients<br>Administer on empty stomach<br>May cause new primary malignancies |
| ***Dasatinib*** | Inhibits BCR-ABL tyrosine kinase | Myelosuppression, fluid retention, diarrhea | CYP3A4 substrates, acid-reducing agents | CBC, BCR-ABL, electrolytes | QT prolongation |
| ***Erlotinib*** | Inhibits EGFR tyrosine kinase | Rash, ILD, hepatoxicity | CYP3A4 substrates, acid-reducing agents, *warfarin* | CMP | Rash equated with increased response |
| ***Ibrutinib*** | Inhibits Bruton tyrosine kinase | Neutropenia, thombocytopenia, diarrhea, anemia, pain, rash, nausea, bruising, fatigue, hemorrhage, pyrexia | CYP3A inhibitors and inducers | CBC, CMP, atrial fibrillation, BP, tumor lysis syndrome | Avoid grapefruit juice and Seville oranges<br>Can cause hepatitis B reactivation<br>Use effective contraceptive |
| ***Idelalisib*** | Inhibits phosphatidylinositol 3-kinase | Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, neutropenia, infection | CYP3A inducers and substrates | CBC, LFTs, pulmonary symptoms, infection | Use effective contraception for female patients |
| ***Imatinib*** | Inhibits BCR-ABL tyrosine kinase | Myelosuppression, fluid retention, CHF | CYP3A4 substrates, *warfarin* | CBC, BCR-ABL | Monitor for development of heart failure |
| ***Nilotinib*** | Inhibits BCR-ABL tyrosine kinase | Myelosuppression, QT prolongation, hepatotoxicity | CYP3A4 substrates, acid-reducing agents | CBC, BCR-ABL, electrolytes | QT prolongation<br>Administer on empty stomach |
| ***Osimertinib*** | Inhibits EGFR tyrosine kinase | Diarrhea, rash, dry skin, nail toxicity, fatigue | Strong CYP3A inducers | CBC, ECG, electrolytes | Use effective contraceptive for female patients |
| ***Pazopanib*** | Multi–tyrosine kinase inhibitor | Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting | CYP3A4 inhibitors, inducers, and substrates; CYP2D6 or CYP2C8 substrates; *simvastatin*; drugs that reduce gastric pH | ECG, electrolytes, thyroid function tests, LFTs, UA, CBC, BP | Use effective contraceptive for female patients |
| ***Sorafenib*** | Inhibits multiple intracellular and cell surface kinases | Hypertension, hand-foot syndrome, rash, diarrhea, fatigue | CYP3A4 inducers, *warfarin* | BP, CMP | Wound healing complications, cardiac events |
| ***Sunitinib*** | Multi–tyrosine kinase inhibitor | Hypertension, hand-foot syndrome, rash, diarrhea, fatigue, hepatotoxicity, hypothyroidism | CYP3A4 substrates | BP, CMP, TSH | Monitor for development of heart failure |
| ***Trametinib*** | Reversible inhibitor of mitogen-activated extracellular kinases | Pyrexia, rash, diarrhea, vomiting, lymphedema | CYP2C8 substrates, P-gp | Fever, new cutaneous malignancies, serum glucose, LVEF, CBC, CMP | Used in combination with *dabrafenib*<br>Administer on empty stomach |
| ***Vemurafenib*** | Inhibits mutated BRAF serine-threonine kinase | Arthralgia, rash, alopecia, fatigue, photosensitivity, pruritus, skin papilloma | CYP3A4 inhibitors and inducers, CYP1A2 substrates | ECG, electrolytes, CMP, uveitis | May cause new primary cutaneous malignancies<br>Use effective contraception in female patients |

# Tyrosine Kinase Inhibitors

The tyrosine kinases are a family of enzymes that are involved in several important processes within a cell, including signal transduction and cell division. The tyrosine kinase inhibitors are administered **orally**, and these agents have a wide variety of applications in the treatment of cancer.

# Immunotherapy

Immunotherapy with intravenous immune checkpoint inhibitors is a rapidly evolving option for cancer treatment. The goal of immune checkpoint inhibitors is to block the checkpoint molecules, such as the programmed death (PD-1) receptor, that normally help to keep the immune system in check.

By blocking these molecules, the immune system is better able to attack the tumor and cause destruction. **The two most commonly used checkpoint inhibitors are pembrolizumab and nivolumab.**

The adverse reaction profiles of these agents consist of potentially severe and even fatal immune-mediated adverse events. This is because turning off the immune checkpoints allows attack of the tumor, but can also lead to unchecked autoimmune response to normal tissues.

**Adverse events include diarrhea, colitis, pneumonitis, hepatitis, nephritis, neurotoxicity, dermatologic toxicity in the form of severe skin rashes, and endocrinopathies such as hypo- or hyperthyroidism.**

Patients should be closely monitored for the potential development of signs and symptoms of toxicity and **promptly treated with corticosteroids if necessary**.

# Miscellaneous Agents

## Abiraterone acetate

Abiraterone acetate is an oral agent used in the treatment of metastatic castration– resistant prostate cancer. Abiraterone acetate is used in conjunction with prednisone to **inhibit** the CYP17 enzyme (an enzyme required for androgen synthesis), resulting in reduced testosterone production.

Coadministration with prednisone is required to help lessen the effects of mineralocorticoid excess resulting from CYP17 inhibition.

Hepatotoxicity may occur, and patients should be closely monitored for hypertension, hypokalemia, and fluid retention. Joint and muscle discomfort, hot flushes, and diarrhea are common adverse effects with this agent.

# Immuno-modulating agents

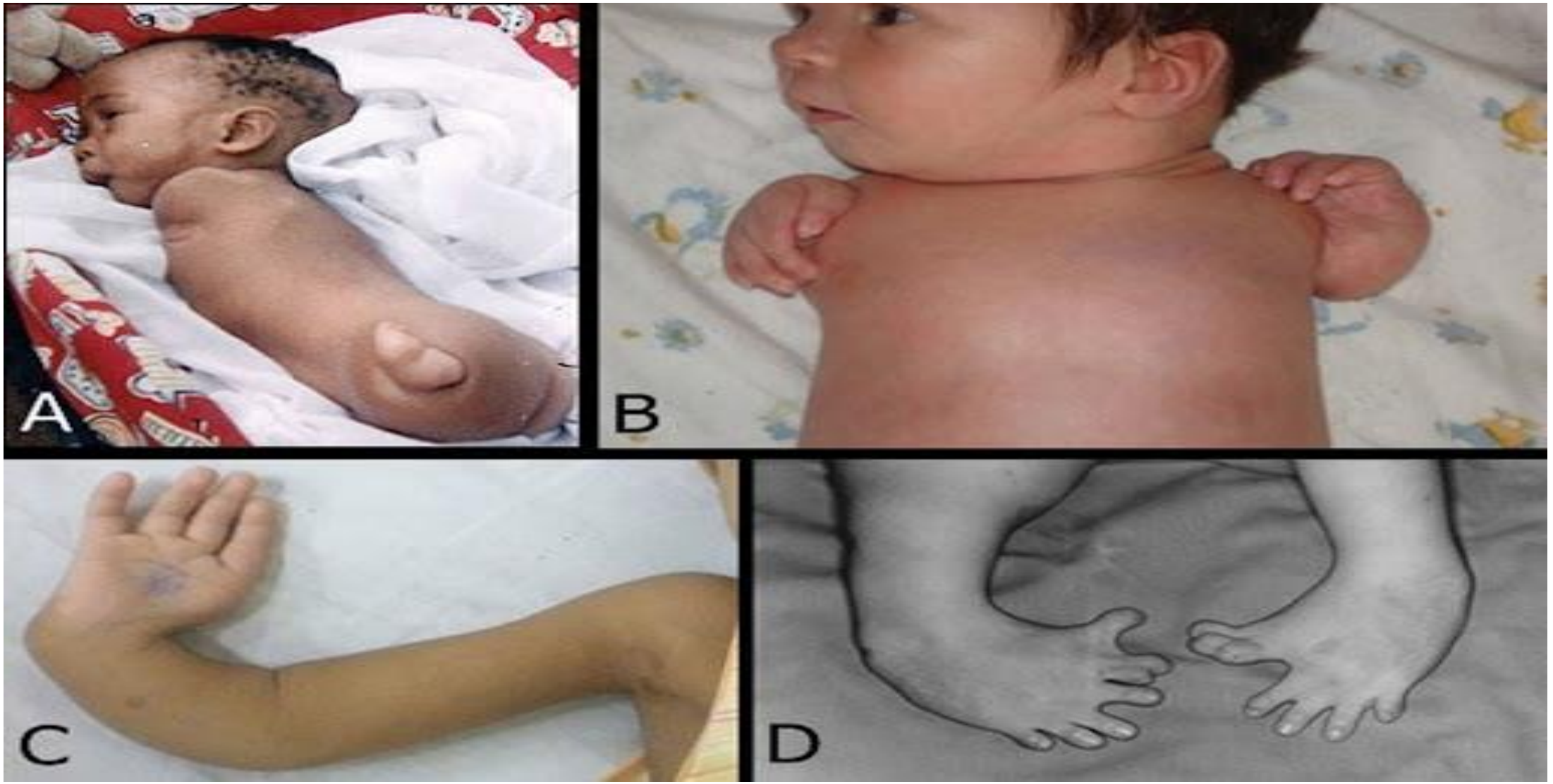
Thalidomide, lenalidomide, and pomalidomide are oral agents used in the treatment of **multiple myeloma**. Their exact mechanism of action is not clear, but they possess antimyeloma properties including antiangiogenic, immune modulation, anti-inflammatory and antiproliferative effects. These agents are **often combined** with dexamethasone or other chemotherapeutic agents.

**Adverse effects include thromboembolism, myelosuppression fatigue, rash, and constipation.**

Thalidomide was previously given to pregnant women to prevent morning sickness. However, severe birth defects were prevalent in children born to mothers who used thalidomide. Because of their structurally similarities to thalidomide, lenalidomide and pomalidomide are contraindicated in pregnancy.

# Immuno-modulating agents

## Thalidomide, lenalidomide, and pomalidomide



# Proteasome inhibitors

Bortezomib, Ixazomib, and Carfilzomib are proteasome inhibitors commonly used as the backbone therapy in the **treatment of multiple myeloma.**

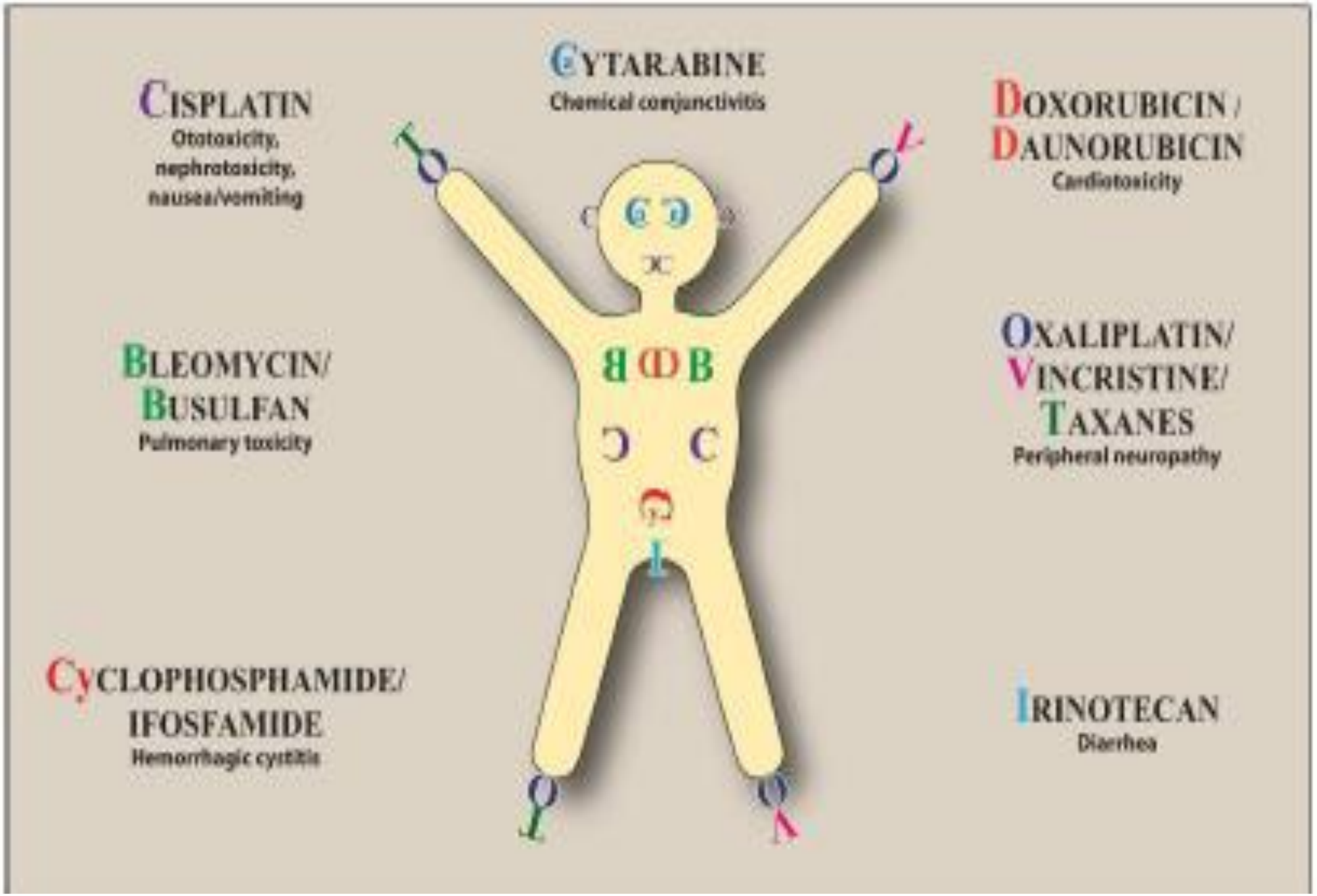
These agents work by inhibiting proteasomes, which in turn prevents the degradation of proapoptotic factors, thus leading to a promotion in programmed cell death (apoptosis).

Malignant cells readily depend on suppression of the apoptotic pathway; therefore, proteasome inhibition works well in multiple myeloma. **Bortezomib can be administered IV, but the subcutaneous route is preferred because it is associated with less neuropathy**.

Other adverse effects include myelosuppression, diarrhea, nausea, fatigue, and herpes zoster reactivation. Patients should receive antiviral prophylaxis if they are receiving therapy with bortezomib.

Ixazomib is an oral agent with an adverse effect profile similar to bortezomib.

Carfilzomib is administered intravenously, and common adverse effects include myelosuppression, fatigue, nausea, diarrhea, and fever.


CISPLATIN
Ototoxicity,
nephrotoxicity,
nausea/vomiting
CYTARABINE
Chemical conjunctivitis
DOXORUBICIN /
DAUNORUBICIN
Cardiotoxicity
BLEOMYCIN/
BUSULFAN
Pulmonary toxicity
OXALIPLATIN/
VINCRISTINE/
TAXANES
Peripheral neuropathy
CYCLOPHOSPHAMIDE/
IFOSFAMIDE
Hemorrhagic cystitis
IRINOTECAN
Diarrhea