Anticancer drugs

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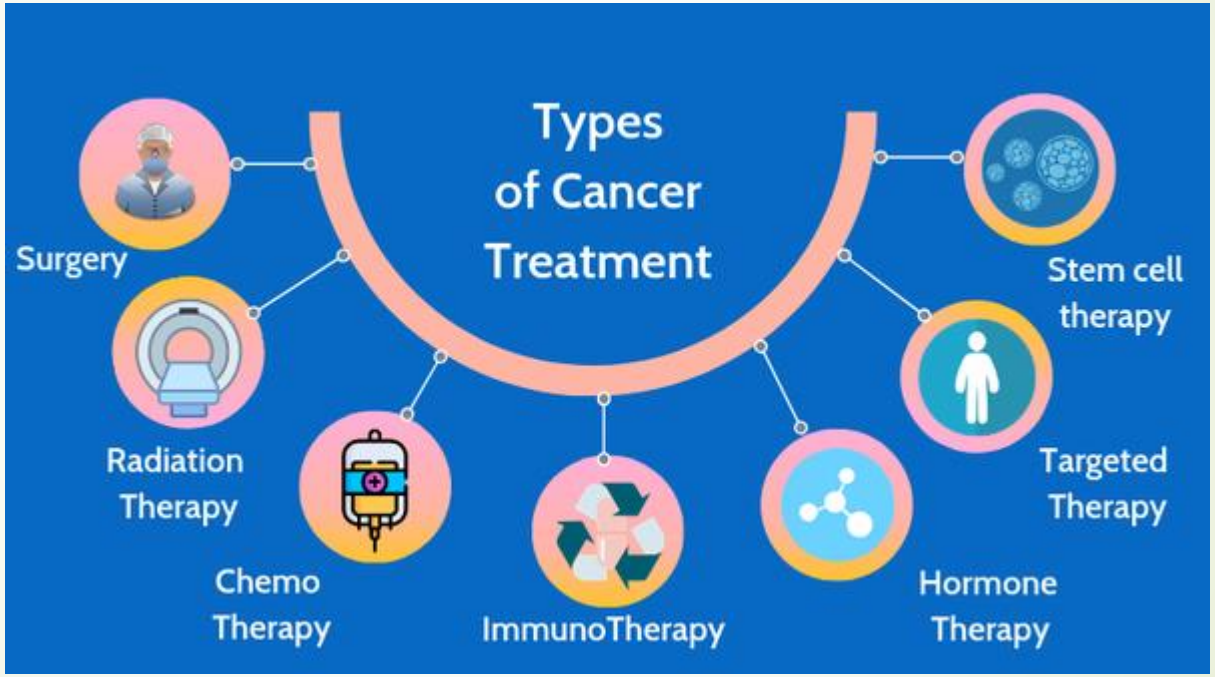
Introduction:

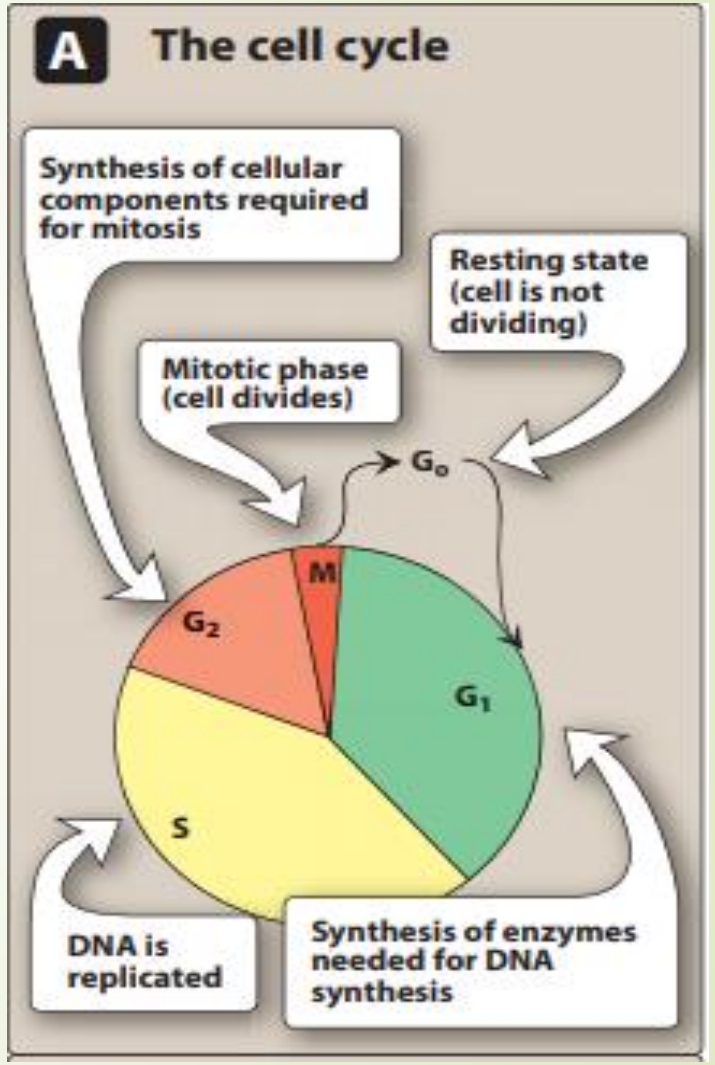
- What is cancer
- What are the treatments of cancer



(https://positivebioscience.com/wp-content/uploads/2019/05/types-of-cancer-treatment.png)

Cancer chemotherapy

- Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cells that can arrest a tumor's progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication, for example, the availability of purines and pyrimidines, which are the building blocks for DNA or RNA synthesis.



Goal of treatment:

- The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life. In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation.

Indications for treatment

- Chemotherapy is sometimes used when neoplasms are disseminated and are not amenable to surgery. Chemotherapy may also be used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, in which case it is called adjuvant chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred to as neoadjuvant chemotherapy, and chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

Treatment protocols

- Combination drug chemotherapy is more successful than single-drug treatment in most of the cancers for which chemotherapy is effective.
- In combinations of drugs, cytotoxic agents with qualitatively 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 non-overlapping host toxicities.
- Advantages of drug combinations: The advantages of such drug combinations are that they 1) provide maximal cell killing within the range of tolerated toxicity, 2) are 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.

Problem associated with chemotherapy

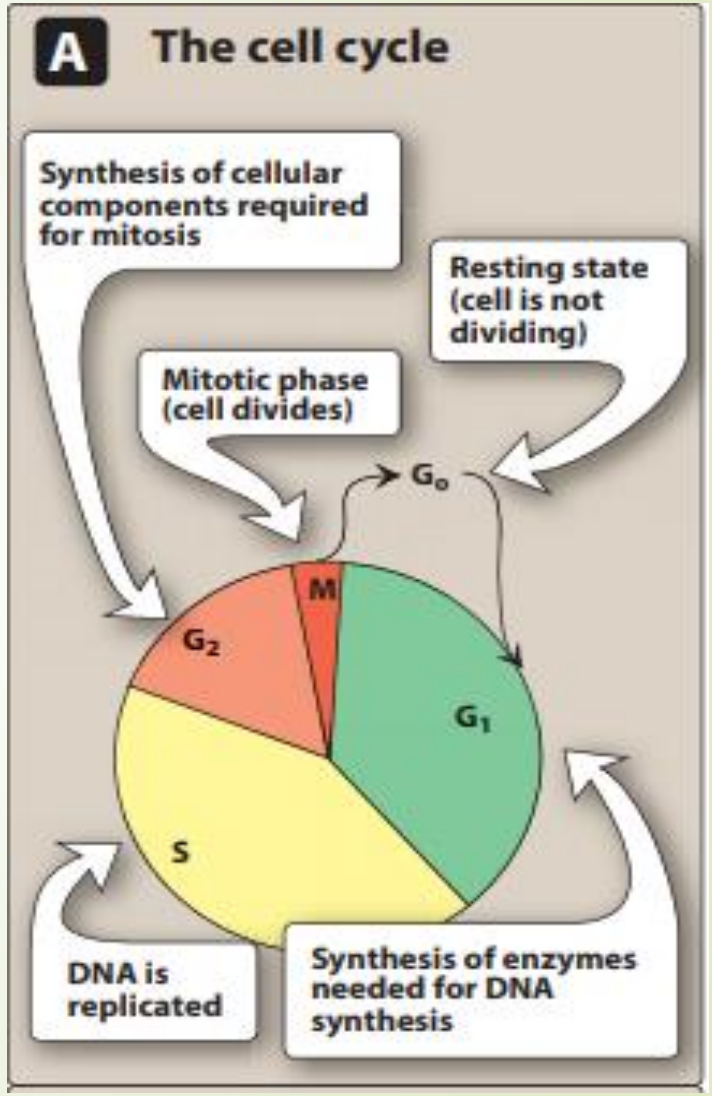
- Resistance: Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a medication by mutating, particularly after prolonged administration of suboptimal drug doses.
- Multidrug resistance: Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for "permeability" glycoprotein) is responsible for multidrug resistance. This resistance is due to adenosine triphosphate– dependent pumping of drugs out of the cell in the presence of P-glycoprotein. Cross-resistance following the use of structurally unrelated agents also occurs.

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 a lesser or greater extent during therapy with all 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.

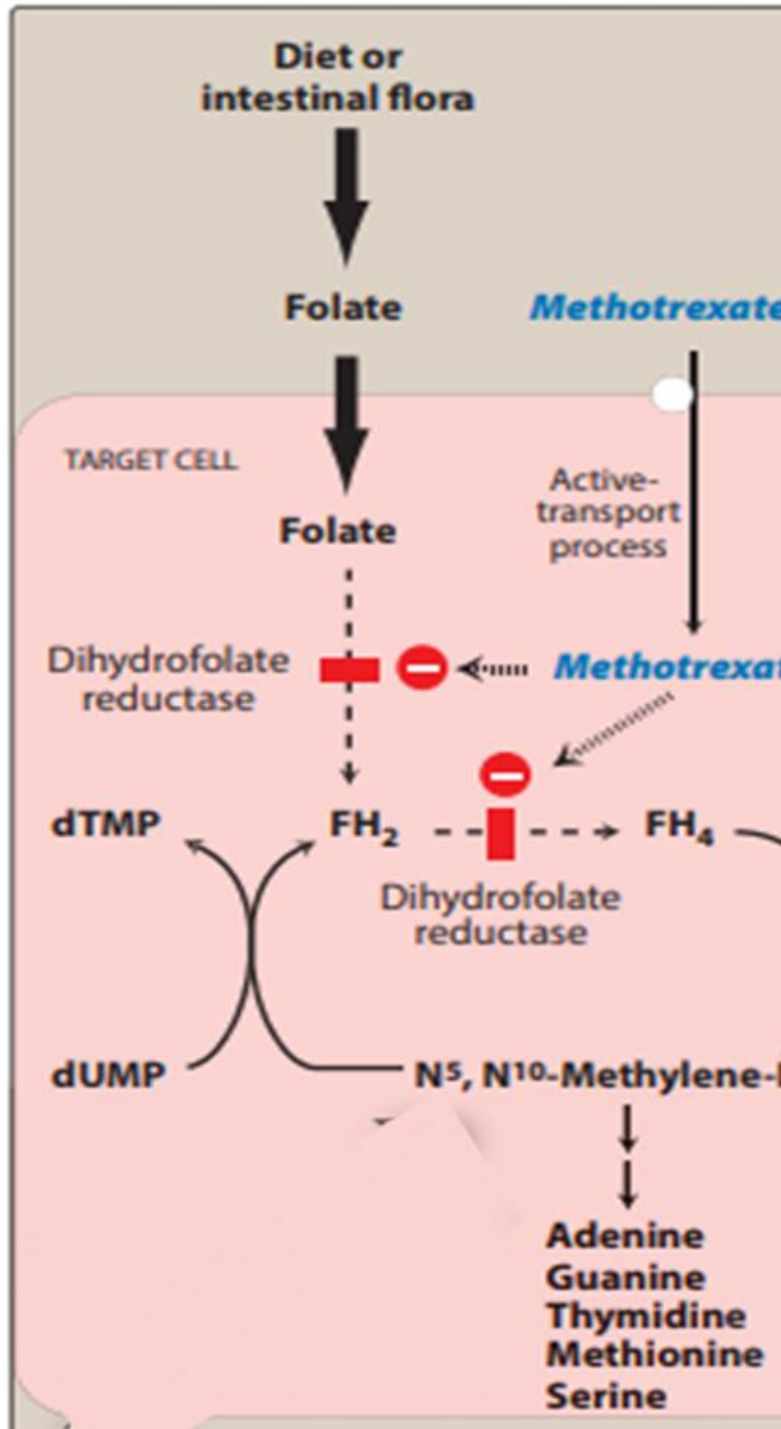
Antimetabolites

- 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.



1- Methotrexate, pemetrexed, and pralatrexate

- Methotrexate (MTX) is a folic acid analog that binds with high affinity to the active catalytic site of dihydrofolate reductase (DHFR). This results in inhibition of the synthesis of tetrahydrofolate (THF) the key one-carbon carrier for enzymatic processes involved in de novo synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine. Inhibition of these various metabolic processes thereby interferes with the formation of DNA, RNA, and key cellular proteins.



Lippincott 7th edition

- Therapeutic uses of methotrexate :
- 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.

2- 6- Mercaptopurine

- Mercaptopurine is a pro-drug that upon entry into the cell it's first converted to thioinosine monophosphate (TIMP). TIMP Inhibits de novo purine nucleotide synthesis. Furthermore, TIMP can be converted into thioguanosine triphosphate (TGTP) which then can be incorporated into RNA, as well as thio-deoxy-guanosine triphosphate (TdGTP) which can be incorporated into DNA thus leading to inhibition of both, DNA and RNA synthesis, resulting in cell death.
- 6-MP is used principally in the maintenance of remission in acute lymphoblastic leukemia. 6-MP is also beneficial in the treatment of Crohn disease.

3- Fludarabine

- Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis.
- It is useful in the treatment of chronic lymphocytic leukemia, hairy cell leukemia, and indolent non-Hodgkin lymphoma.

4- Cladribine

- Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis.
- Cladribine is effective against hairy cell leukemia, chronic lymphocytic leukemia.

5- 5-Fluorouracil

- Inhibits thymidine synthase; incorporation of 5-fluorouracil metabolite 5-fluorouridine-triphosphate into RNA resulting in alteration in RNA processing; incorporation of the other metabolite 5-fluorodeoxyuridine-5'-triphosphate into DNA resulting in inhibition of DNA synthesis and function.
- 5-FU is employed primarily in the treatment of slowly 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.
- Capecitabine orally active drug that transform into 5-FU after absorption.

6- Cytarabine

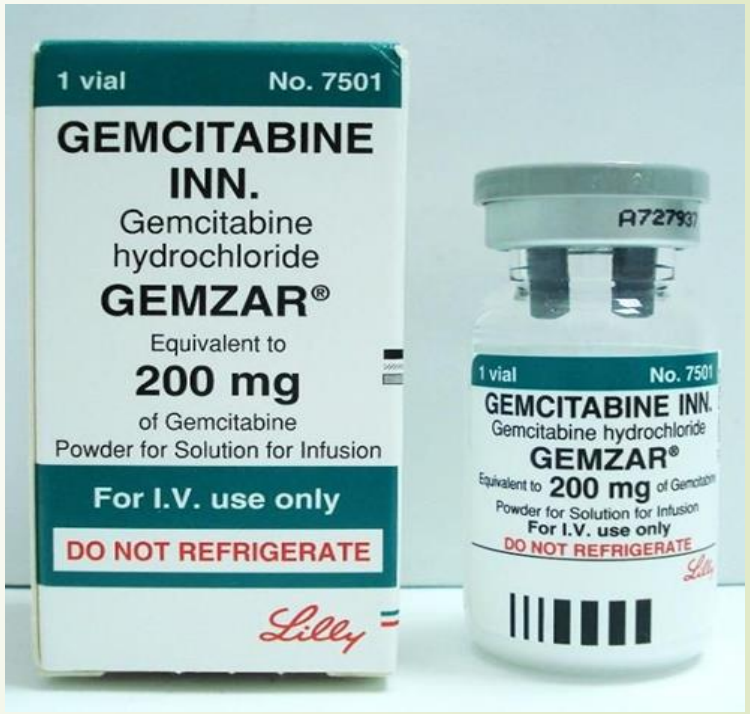
- Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of deoxyribonucleotide triphosphate; incorporation of cytarabine triphosphate into DNA.
- The major clinical use of cytarabine is in acute non-lymphocytic (myelogenous) leukemia

7- Azacitidine

- Azacitidine undergoes activation to the nucleotide metabolite azacitidine triphosphate and gets incorporated into RNA to inhibit RNA processing and function.
- It is used for the treatment of myelodysplastic syndromes and leukemia

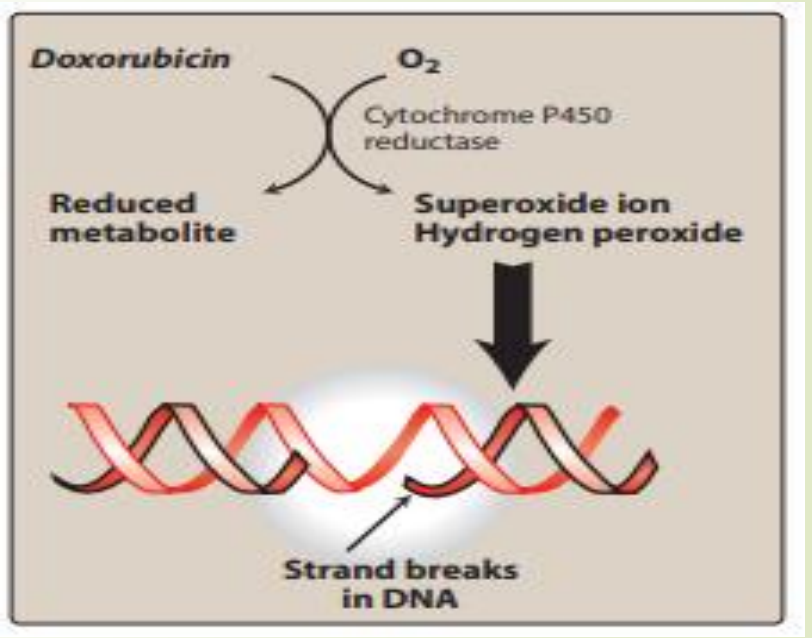
8- Gemcitabine

- Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of deoxyribonucleotide triphosphate; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function.
- It is used most commonly for pancreatic cancer and non– small cell lung cancer



Antibiotics

- 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.



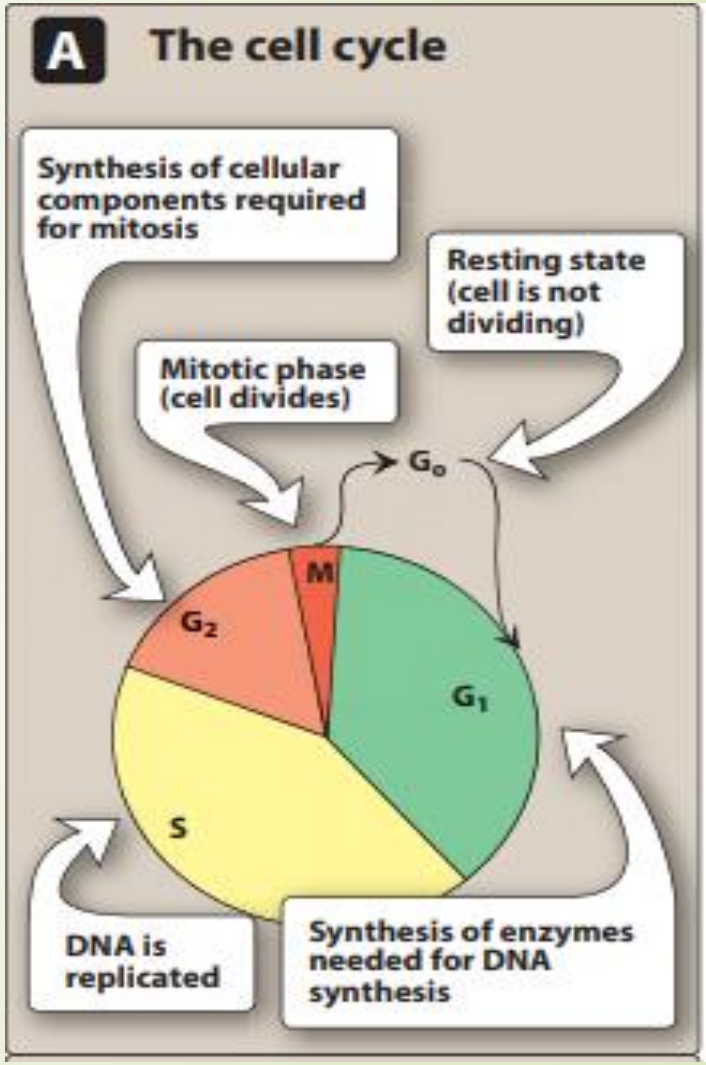
Doxorubicin interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.

1- Anthracyclines: Doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone

- Doxorubicin is one of the most important and widely used anticancer drugs. It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast and lung, 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.
- 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

2- Bleomycin

- It 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.

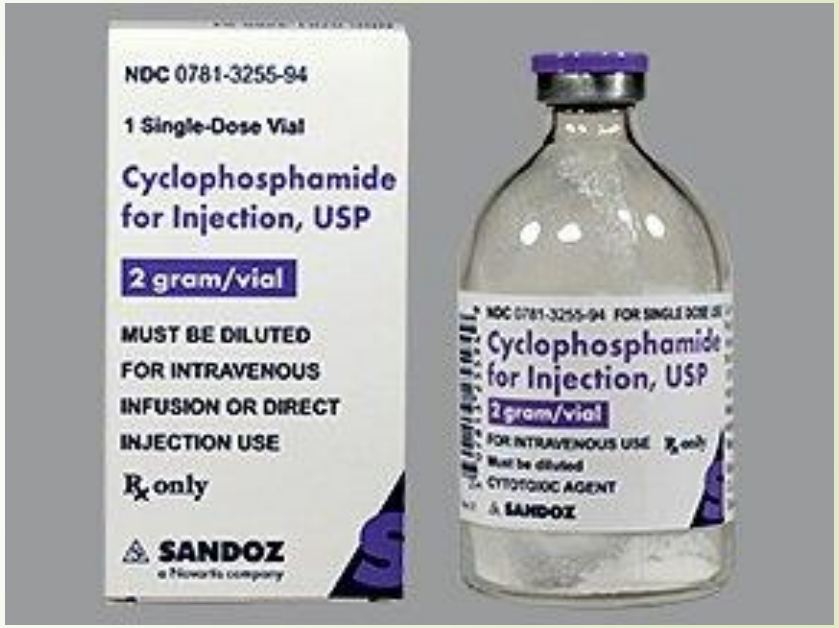


Alkylating agents

- Act by transferring alkyl groups to DNA in the N-7 position of guanine during cell division. There follows either DNA strand breakage or crosslinking of the two strands so that normal synthesis is prevented. Alkylating agents do not discriminate between cycling and resting cells, even though they are most toxic for rapidly dividing cells.
- All are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

1- Cyclophosphamide and ifosfamide

- Forms DNA cross-links, resulting in inhibition of DNA synthesis and function.
- These agents have a broad clinical spectrum, being used either singly or as part of a regimen in the treatment of a wide variety of neoplastic diseases, such as non-Hodgkin lymphoma, sarcoma, and breast cancer



2- Nitrosoureas

- The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis.
- Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors.
- Carmustine and lomustine

3- Dacarbazine

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

4- Temozolomide

- It methylate DNA on the 6 position of guanine
- Temozolomide also has the property of inhibiting the repair enzyme, O6 -guanine-DNA alkyltransferase.
- has been approved for use against glioblastomas and anaplastic astrocytomas. It is also used in metastatic melanoma.

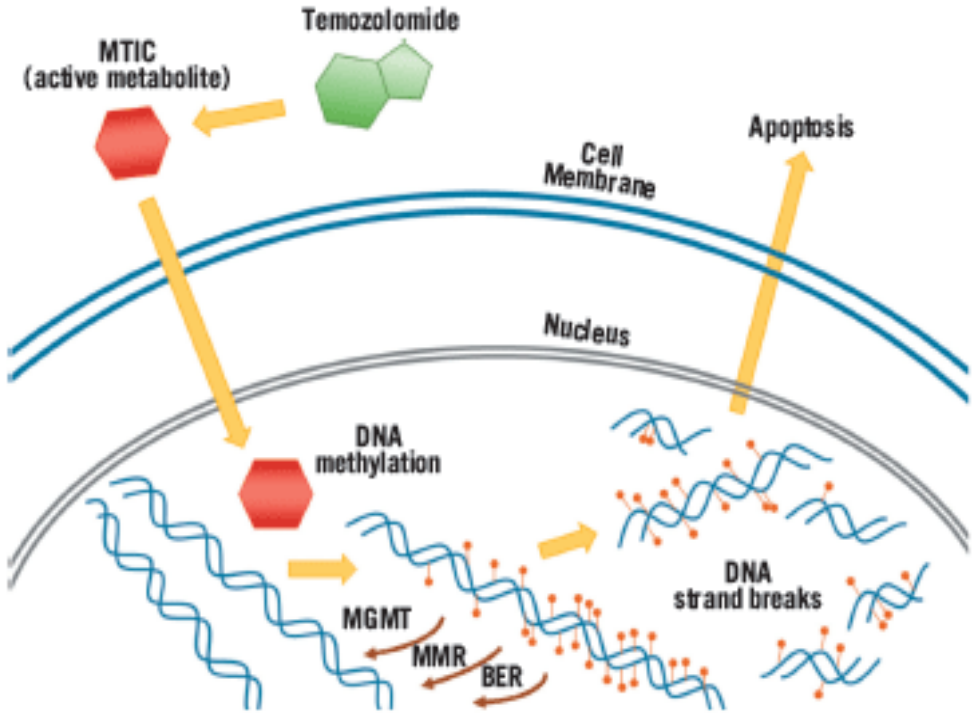
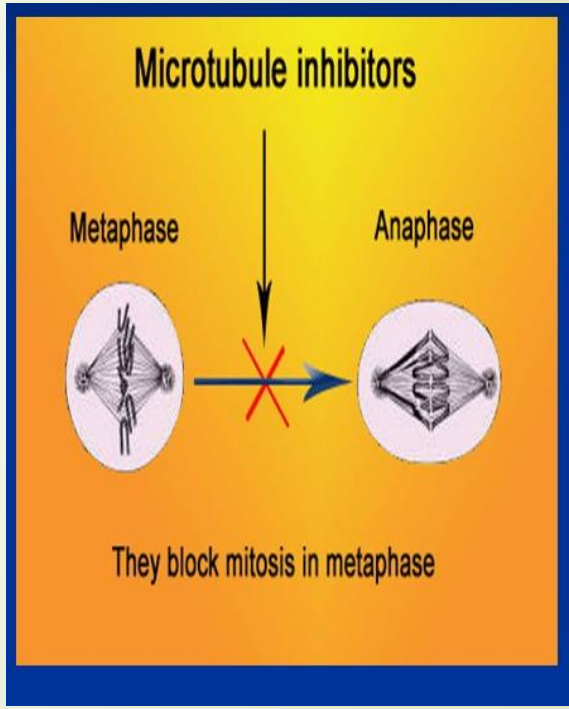


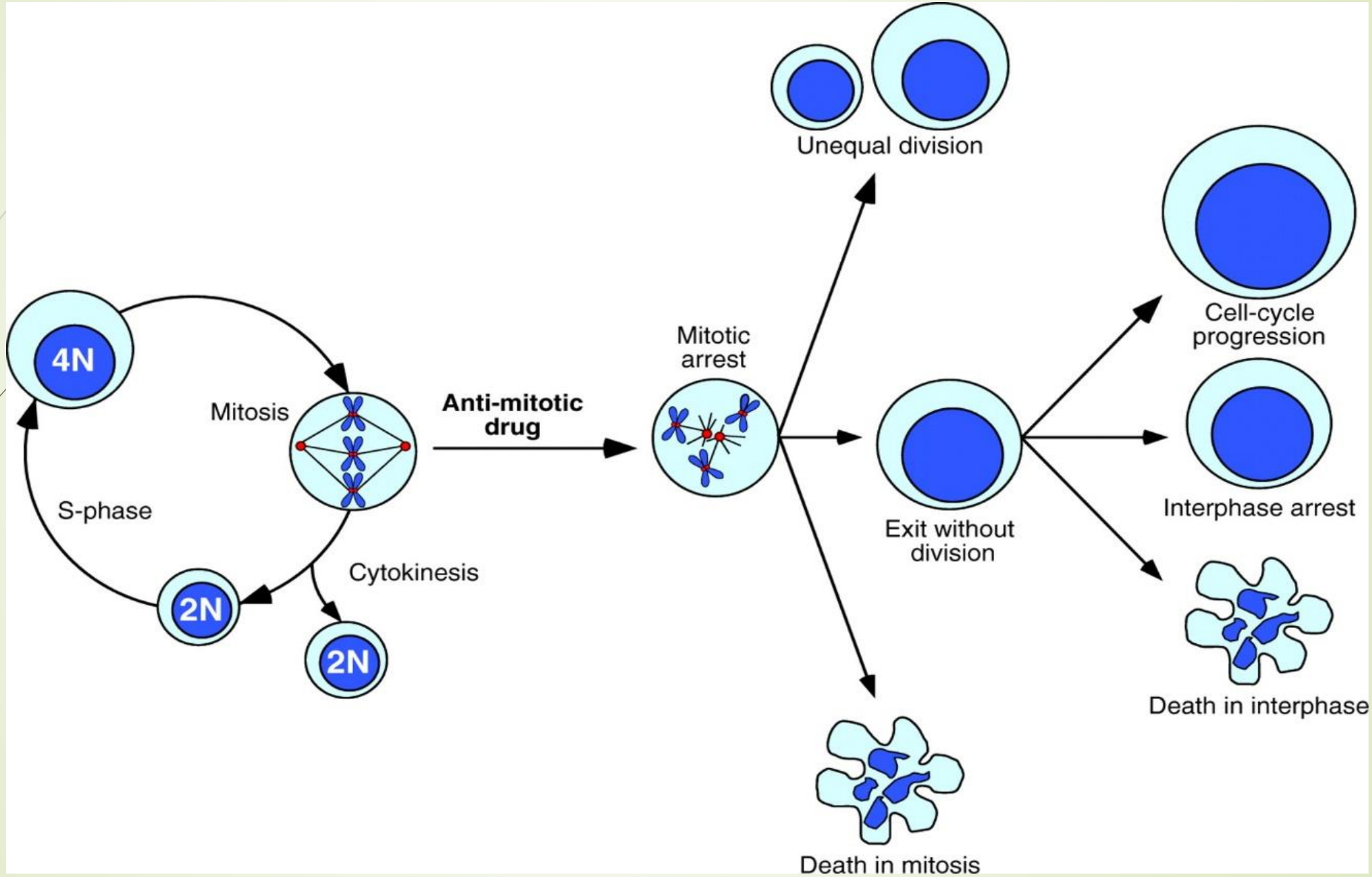
FIGURE Temozolomide's Mechanism of Action—Temozolomide is spontaneously hydrolyzed to its active metabolite, MTIC, which translocates into the nucleus. There, it transfers methyl groups on to guanine, causing double-strand DNA breaks during replication and leading to apoptosis. Its actions are opposed by intranuclear DNA repair mechanisms, including MGMT, MMR, and BER.

BER = base excision repair; MGMT = O6-methylguanine-DNA methyltransferase; MMR = mismatch repair; MTIC = 3-methyl-(triazen-1-yl)imidazole-4-carboxamide.

Microtubule inhibitors

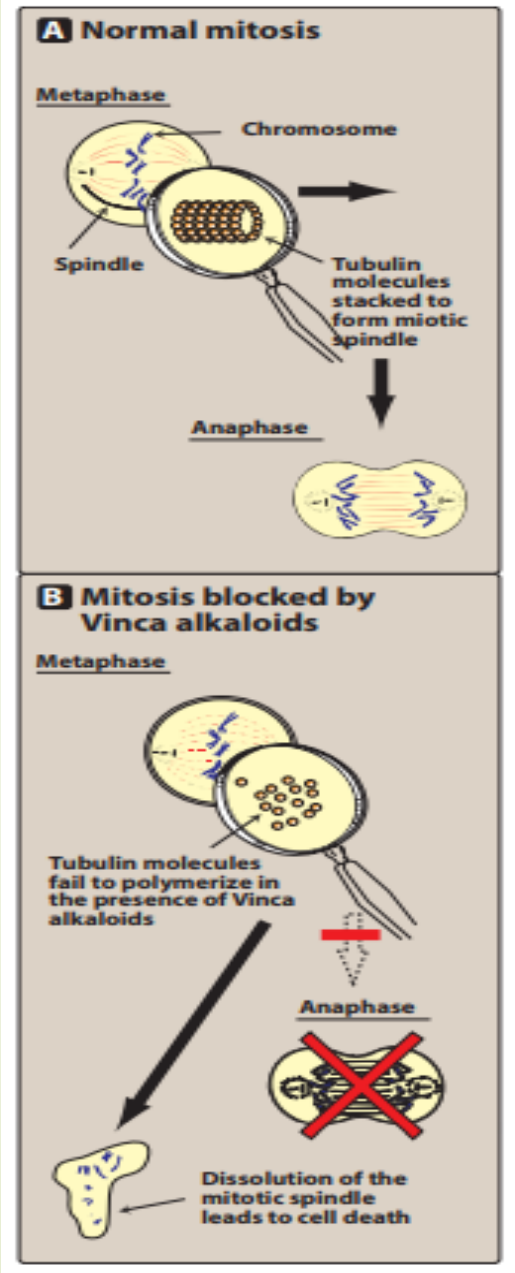
- The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity.




4N
Mitosis
S-phase
Cytokinesis
2N
2N
Anti-mitotic drug
Mitotic arrest
Unequal division
Cell-cycle progression
Interphase arrest
Exit without division
Death in interphase
Death in mitosis

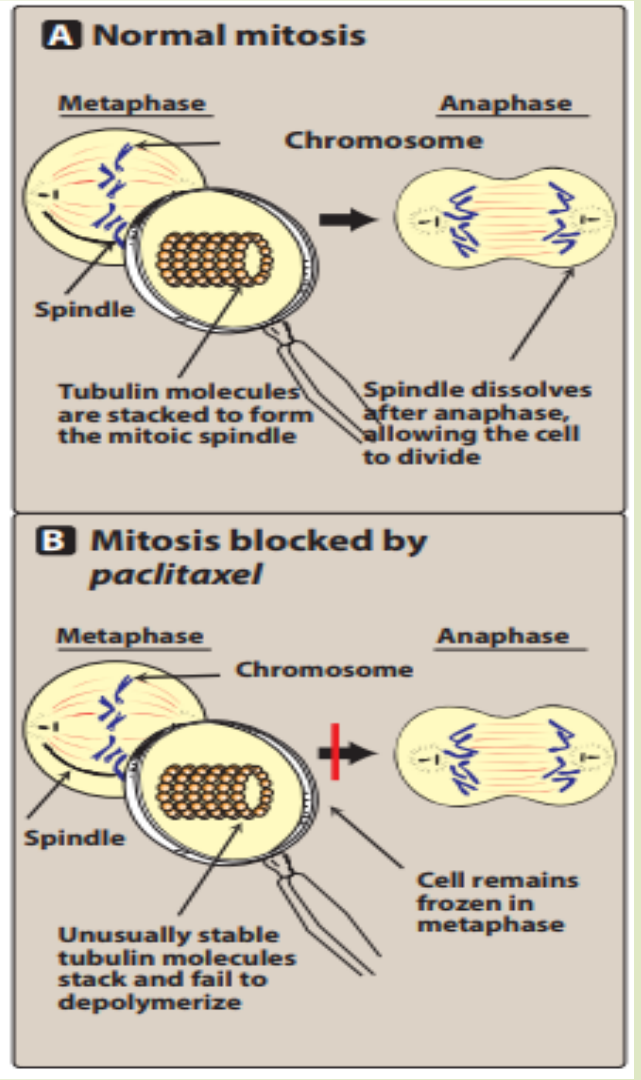
1- Vincristine and vinblastine (Vinca Alkaloids)

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



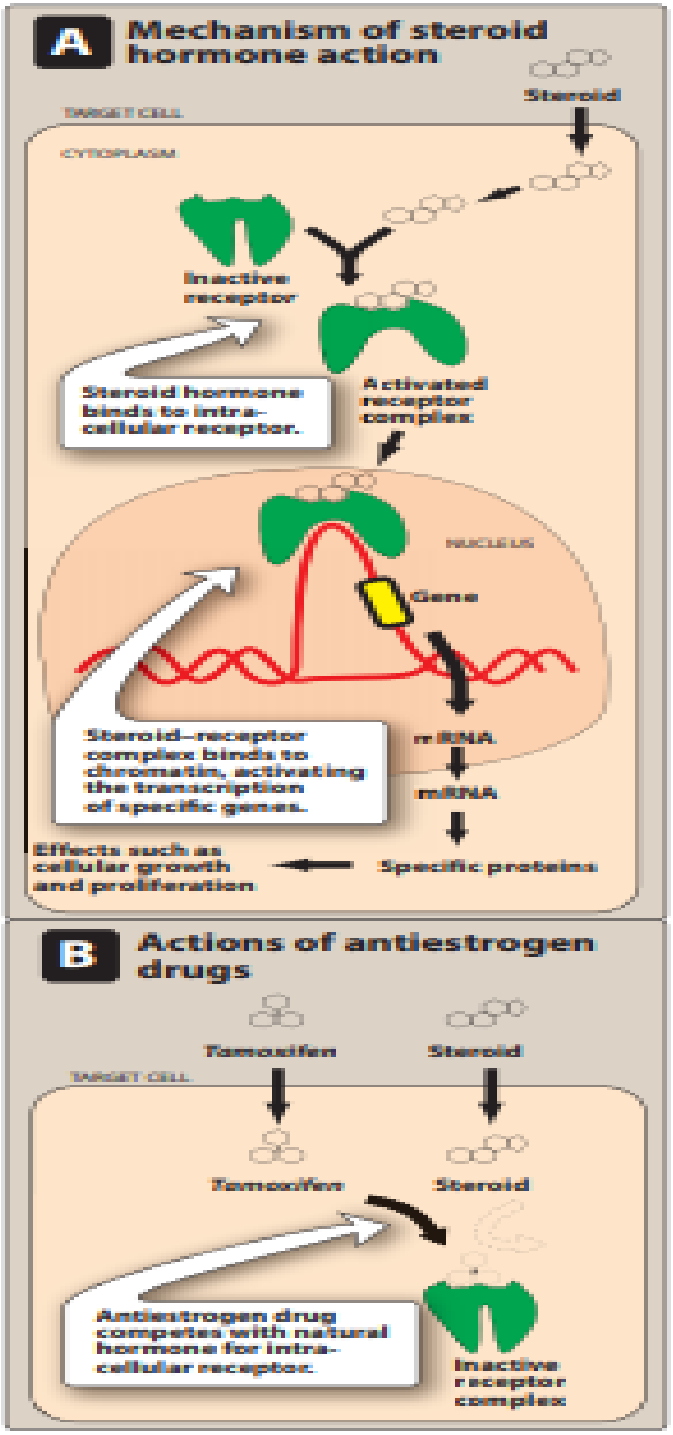
2- Paclitaxel and docetaxel

- 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 overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell.
- Paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer. Favorable results have been obtained in non–small cell lung cancer when administered with cisplatin. Docetaxel is commonly used in prostate, breast, GI, and non–small cell lung cancers.



Steroid Hormones and their antagonists

- Tumors that are steroid hormone sensitive may be either
- 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone.
- 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression.
- 3) both.



1- Prednisone

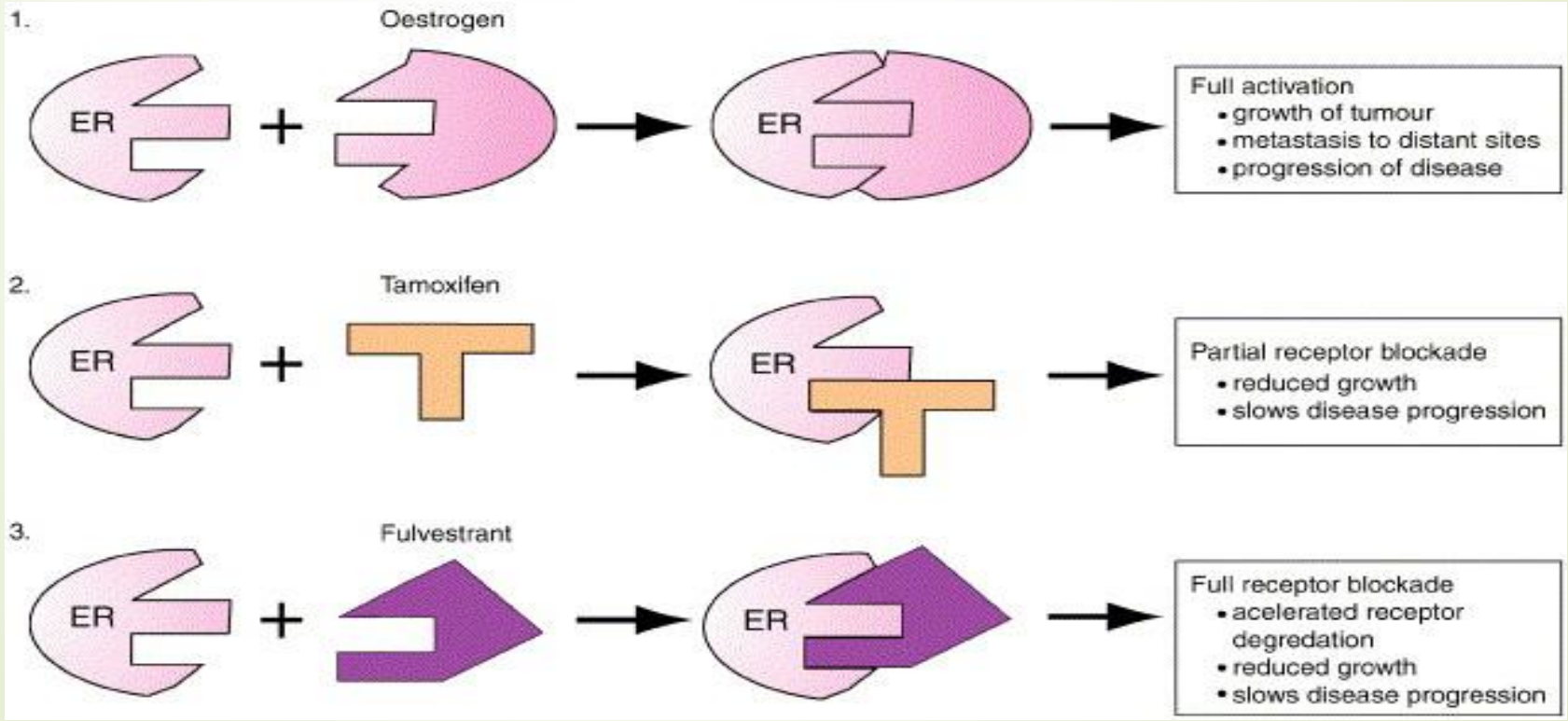
- Prednisone is primarily employed to induce remission in patients with acute lymphocytic leukemia and in the treatment of both Hodgkin and non-Hodgkin lymphomas.

2- Tamoxifen

- It is used for first-line therapy in the treatment of estrogen receptor–positive breast cancer. It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk.
- Tamoxifen is an estrogen antagonist with some estrogenic activity, and it is classified as a selective estrogen receptor modulator

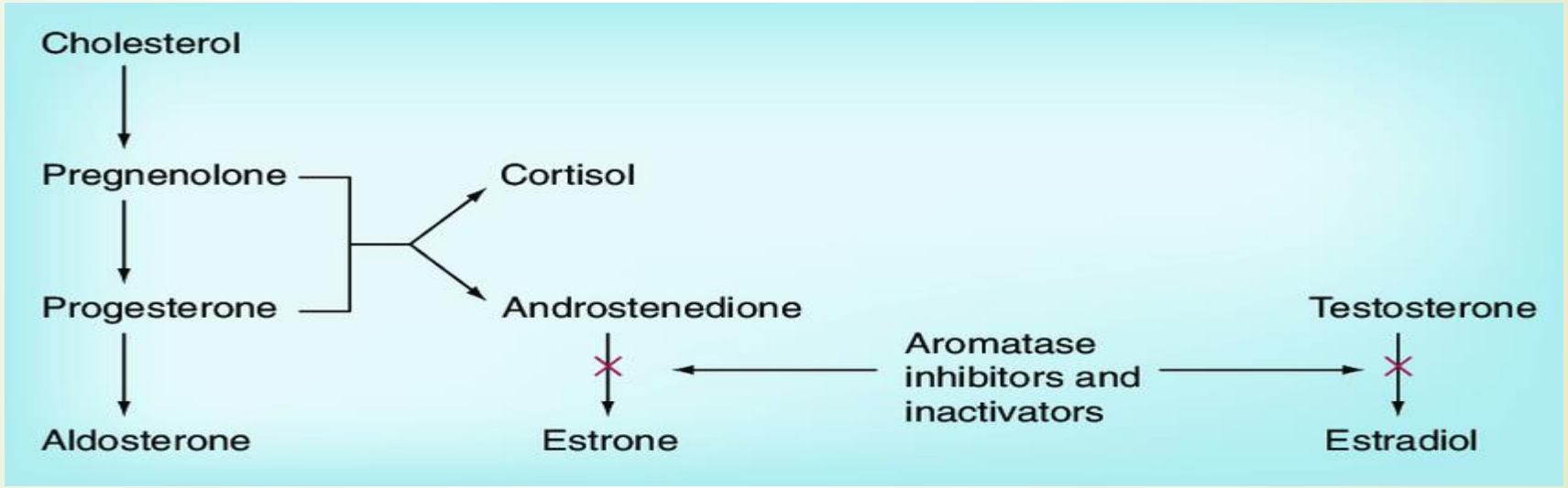
3- Fulvestrant and raloxifene

- Fulvestrant is an estrogen receptor antagonist, used to treat metastatic breast cancer.
- Raloxifene is a selective estrogen receptor modulator, it block estrogen effects in the uterine and breast tissues.



4- Aromatase inhibitors

- Aromatase inhibitors decrease the production of estrogen in post-menopausal women.



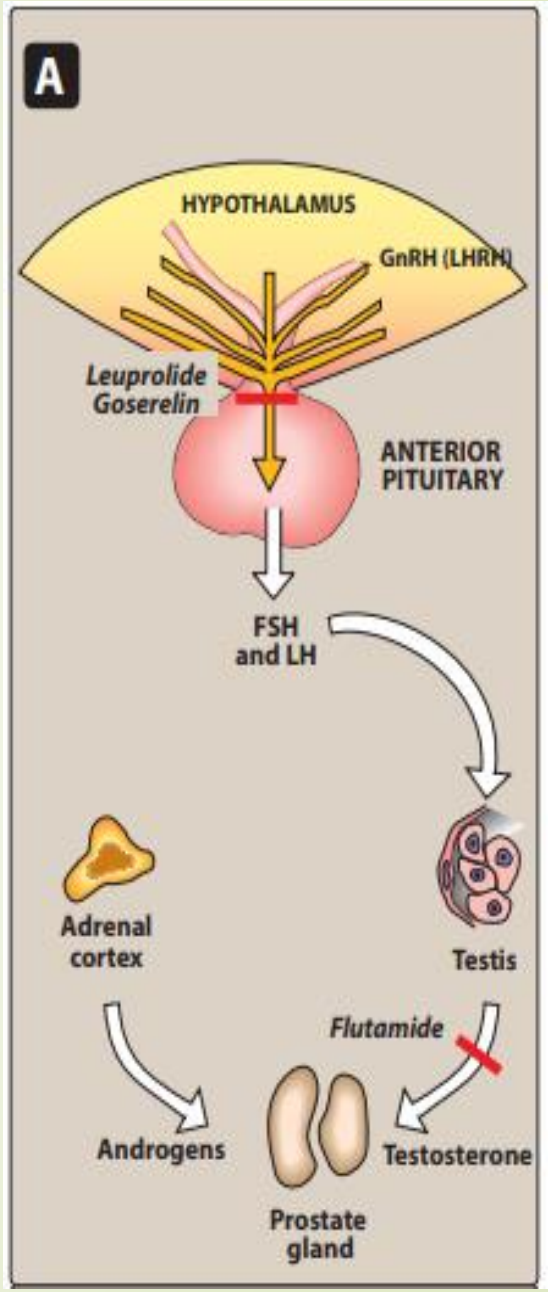
- Examples are: Anastrozole, letrozole, and Exemestane.

5- Leuprolide, goserelin, and triptorelin

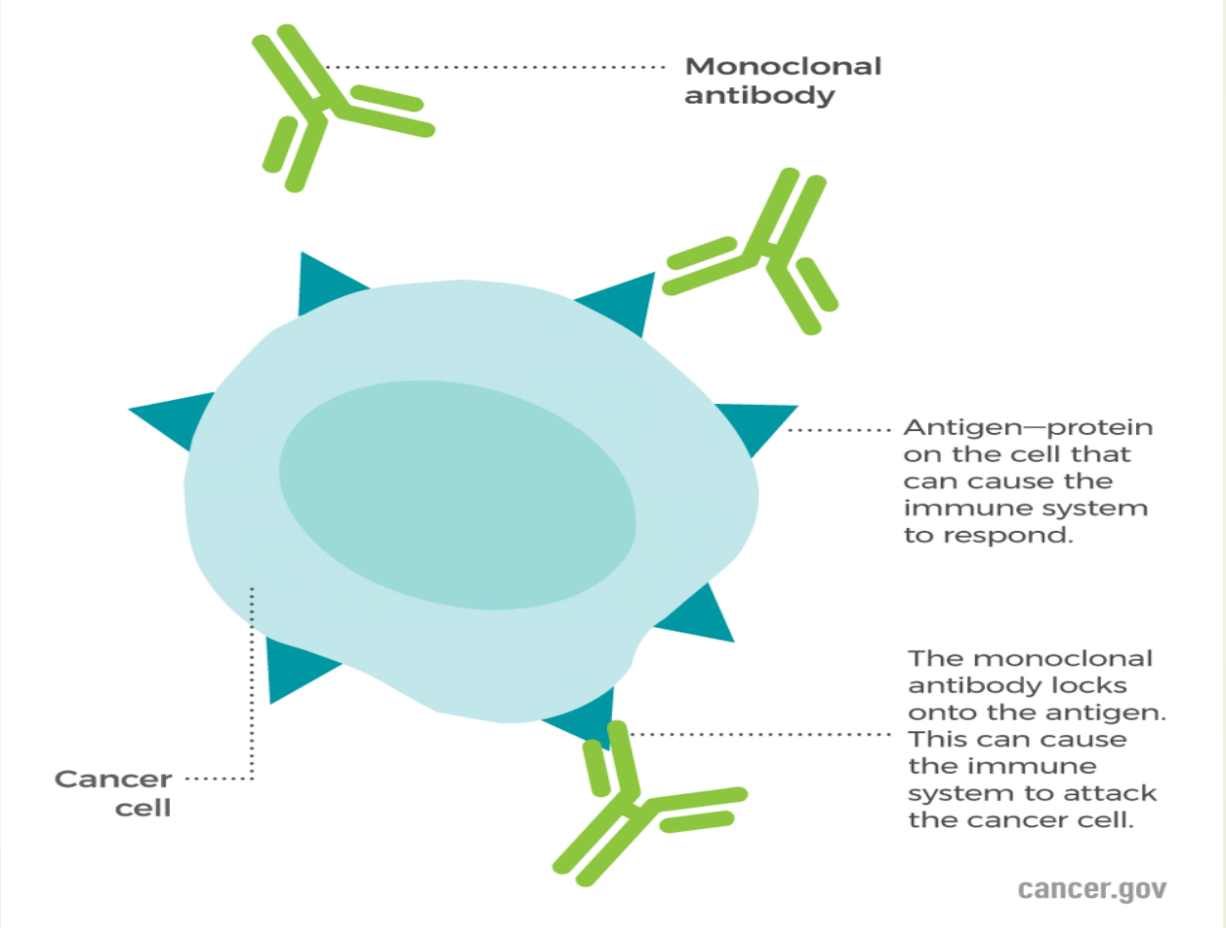
- All 3 drugs are As Gonadotropin-releasing hormone GnRH analogs, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen syntheses are reduced.

6- Flutamide, nilutamide, and bicalutamide

- They compete with the natural hormone for binding to the androgen receptor and prevent its translocation into the nucleus.
- used in the treatment of prostate cancer



Monoclonal antibodies

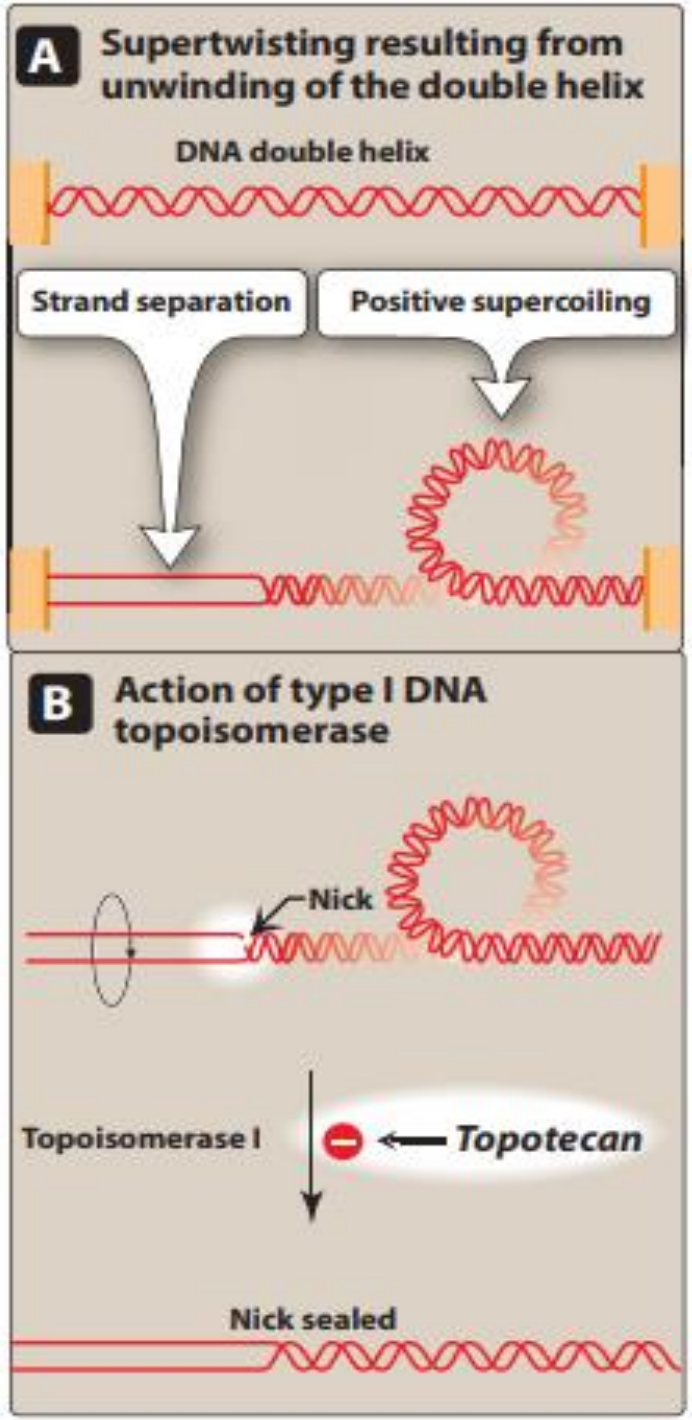


Platinum coordination complexes

- Cisplatin, carboplatin, and oxaliplatin
- Treatment of solid tumors, such as metastatic testicular carcinoma in combination with vinblastine and bleomycin, ovarian carcinoma in combination with cyclophosphamide, or alone for bladder carcinoma.
- It binds to guanine in DNA, forming inter- and intrastrand crosslinks. The resulting cytotoxic lesion inhibits both polymerases for DNA replication and RNA synthesis.

Topoisomerase inhibitors

- These agents exert their mechanism of action via inhibition of topoisomerase enzymes, a class of enzymes that reduce supercoiling of DNA.
- Topoisomerase inhibitors I Include Camptothecins, Irinotecan, and topotecan.
- 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.
- Topoisomerase inhibitors II Include etoposide which is used in the treatment of lung cancer and in combination with bleomycin and cisplatin for testicular carcinoma



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. Many tyrosine kinase inhibitors are available.
- Imatinib, dasatinib, and nilotinib: treatment of chronic myelogenous leukemia (CML) as well as GI stromal tumors.
- Erlotinib: treatment of non–small cell lung cancer and pancreatic cancer.
- Sorafenib and sunitinib: treatment of renal cell carcinoma. Sorafenib is also part of the treatment strategy for hepatocellular carcinoma, and sunitinib is used in GI stromal tumors and pancreatic neuroendocrine tumors.

Miscellaneous Agents

- Procarbazine: treatment of Hodgkin disease and other cancers.
- Asparaginase and pegaspargase: o treat childhood acute lymphocytic leukemia in combination with vincristine and prednisone.
- Interferons: Interferon-a-2a is currently approved for the management of hairy cell leukemia, chronic myelogenous leukemia, and acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma. Interferon-a-2b is approved for the treatment of hairy cell leukemia, melanoma, AIDS-related Kaposi sarcoma, and follicular lymphoma.
- Abiraterone acetate: metastatic castration–resistant prostate cancer.
- Enzalutamide: treatment of metastatic castrate-resistant prostate cancer in patients that have previously received docetaxel chemotherapy.

Thank you for listening