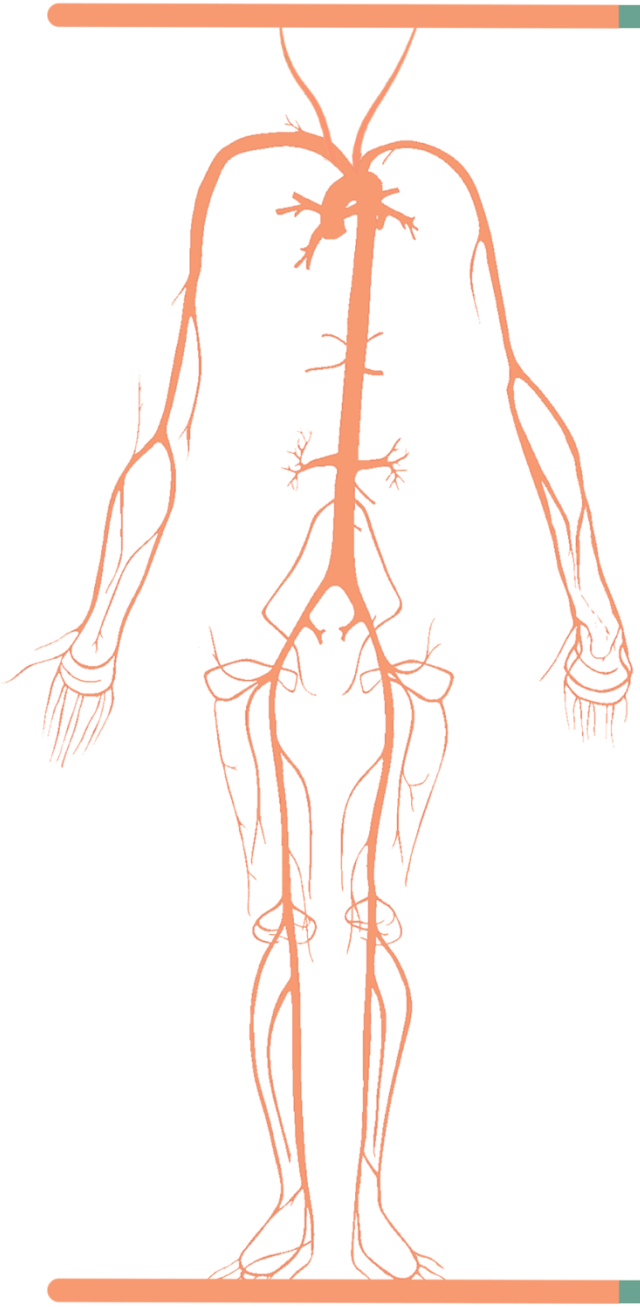
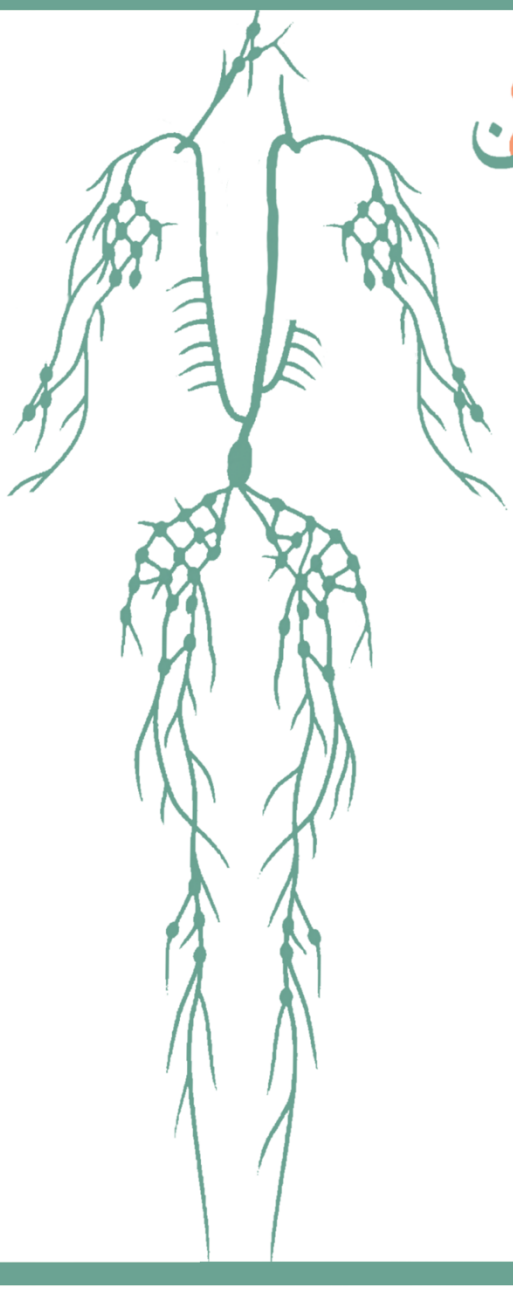
Pharmacology

HematoLymphatic





Title: Sheet 6 – Cancer Chemotherapy

Writer: 018 - Updated by 019

Scientific Correction: Anas Zayad & Mohammed Hatamleh

Final Correction: Dana Alnasra

Doctor: Munir Gharaibeh

In this lecture we're going to talk about cancer chemotherapy.

➢ Modalities of Cancer Chemotherapy:

1. **Curative:**
   - It is a limited treatment for malignancies as only 10-15% of cancers can be completely or permanently cured by introducing chemotherapy.
   - Although this is a low percentage, it is very significant and very useful.
   - Used in certain disseminated neoplasms. (The more the neoplasm is disseminated like in cases of leukemia, the more it can be eradicated, because it is free in the circulation and can be tackled by chemotherapeutic agents).
2. **Palliative:**
   - Given only to relieve the symptoms temporarily and enhance the overall quality of life, not to cure the cancer.
   - It doesn't prevent or delay death but enhances quality of life before death.
3. **Adjuvant:**
   - Given as an adjuvant to surgery, even if there is no evidence of metastasis.
   - 85-90% of cancer cases are treated surgically, so we can help surgery with Adjuvant treatment as it helps in tumor shrinkage and eradicating the remaining tumor cells that surgery didn't get rid of.

➢ Classes of Anticancer Drugs: **((the doctor said don't memorize them))**

-Signal Transduction Inhibitors. - Microtubule Inhibitors. -Differentiation agents.
-Antimetastatic Drugs. -Antiangiogenic drugs. -Hypoxic Tumor Stem Cell- specific.
-Tumor Radiosensitizing. -Normal Tissue Radioprotecting Drugs.
-Cytoprotective Agents. -Biologic Response Modifiers.

➢ The Ideal Anticancer Drugs:

- Most of cancer drugs are not ideal; they have many Side effects, they don't have great efficacy and they are not 100% effective, unlike hypersensitivity drugs, antimicrobial drugs and peptic ulcer drugs.
  BUT the ideal anti-cancer drug should:

1. **Exploit the differences between normal and tumor cells:**
   -If the anticancer drug can differentiate between normal and tumor cells then this is of great advantage, but if it doesn't then we expect the drug to have many side effects.

2. **Broad spectrum of activity:**
   -Meaning that the drug can affect many tumor cells.

3. **Good distribution through the body.**

4. **Non-immunogenic.:**
   - Doesn't cause hypersensitivity or allergic reaction.
   - Doesn't affect the immune system or suppress it.

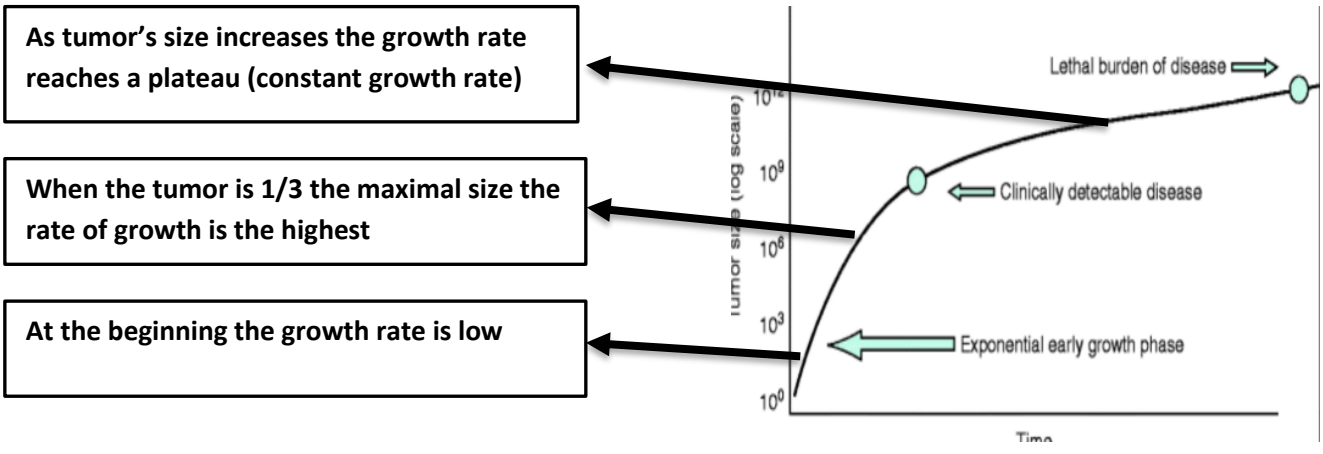
5. **Adequate biological half-life.**
6. **Reasonably priced.**

But unfortunately, **current anticancer drugs are:**

1. **Carcinogenic**.:
- Although they can treat cancer, but they also can induce cancer.
2. **Mutagenic**:
- They can cause mutations in the cell.
3. **Teratogenic**:
- They can cause birth defects in fetuses.
4. **Immunosuppressive**:
- They suppress the immunity so patients will develop superinfections.
5. **Very toxic:**
- Anticancer drugs are very sensitive compared to other drugs.
- Tolerance can develop.

➢ Gompertzian Tumor Growth:

- Tumor's growth follows Gompertzian principle. this principle states that:
  a) The growth rate of a tumor is not constant (the growth follows a curve)
  b) The highest growth rate of tumor is achieved when the tumor size is one third of its maximal size. (the growth rate peaks when the tumor is 1/3 the maximal size).
- So, at the beginning the growth is slow, then it reaches a peak when the tumor is one third the maximal size (exponential growth), then the growth slows down again (plateau).

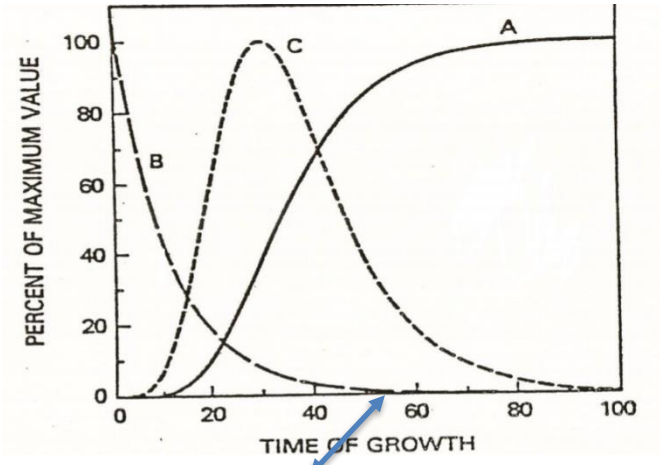


This curve shows ***Norton- Simon relationship*** between:

A: tumor size (the previous carve)

B: instanteous growth fraction (IGF): percentage of cells engaged in proliferation to cells in G0 phase at any given point of time.

IGF is 100% at the beginning and then it starts to decrease until it reaches zero, and at that point, the tumor is in the maximal size.



The point when instanteous growth fraction reaches 0 (B) when the maximal size of tumor reached. (A)

C: growth rate is highest at the first third, then it starts to slow down.

➢ Log-Kill Hypothesis (Exponential Cell Kinetics):

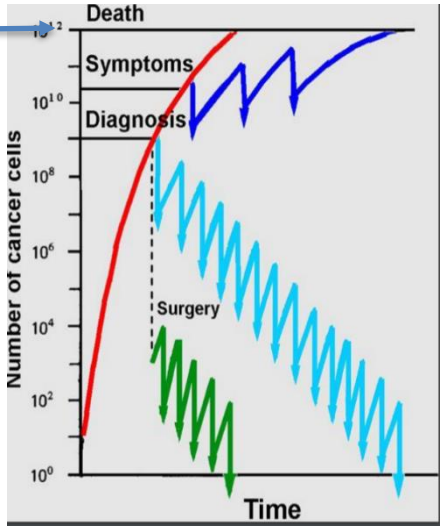
Drugs can kill tumor cells by Exponential Cell Kinetics mechanisms, and we call this Log-Kill Hypothesis, (Exponential curve means that the curve follows the logarithmic scale).

Let's take an example:

In acute leukemias and aggressive lymphomas:

- Number of cells at time of diagnosis: 10^12 cells
- Let us assume that we have very effective drug that can kill 99.99% of tumor cells.
- If we apply Log-Kill Hypothesis the cells in remission will be 10^8 (the drug kills 10^4 tumor cells only).
- We also have to add to those 10^8 cells: 1-the number of cells that are inherently resistant (the 99.99% is for sensitive cells) 2-cells not available for the drug (CNS, testes) 3-and cells in the G0 phase (cells in G0 phase are insensitive or less sensitive for drugs). So, we will have even more than 10^8 tumor cells in remission.

- The example shows the effects of tumor burden (number of cells), scheduling, initiation/duration of treatment on patient survival.
- The red line shows the tumor burden (number of tumor cells without any intervention).
- Number of cells at the time of diagnosis usually equal 10^9 (The diagnosis is made via conventional methods)
- the patient is symptomatic when the number of tumor cells exceed 10^10 or 10^11 cells, and death occurs when the number of tumor cells is 10^12.
- If we start treatment when symptoms appear, usually chemotherapeutic agents are not effective, and what we do is just giving **Palliative drugs.**
- If surgery is indicated, then we are able to drop the number down to 10^3 (green line), after that we start treatment with chemotherapeutic agents to reduce the number of cancer cells to a very minimal number.
- However, if surgery is not indicated (like in leukemia), we do not have any choice other than chemotherapeutic agents, and that would require many cycles to achieve approximate cure. (light blue line).



➢ Combination Chemotherapy

- There is no single drug to treat tumors, so usually drugs are given in combinations
- The combination therapy aims to:
    1. Increase effectiveness.
    2. Reduce the toxicity.
- Employed to overcome the limited log-kill of individual drugs.
- The drugs should be effective when used as single agents, and when combined, their effectiveness increases.
- If there is no biochemical basis for synergism, there should be at least additive effects. (synergism is preferable).
- where possible, drugs with differing modes of action are combined. (when the drugs work in two different mechanisms, they synergize each other).
- The major toxicity of each drug should be as different as possible from that of the other agents (non-overlapping toxicity), minor toxicities of each combined drug are accepted.
- Toxicity appears at different times; this gives us a chance to handle each toxicity separately.

- **Myelosuppressant** & **nonsuppressant**, (if one drug is Myelosuppressant the other drug should not be Myelosuppressant, otherwise, this will make additive toxic effects, resulting in more bone marrow suppression).
- Usually, treatment of cancer by cytotoxic drugs is given in repeated courses arranged so that the recovery of normal cells can occur, but little recovery of cancer cells is possible, so we do not give the patient large doses of these drugs even if they have high effectivity, because they will damage and kill normal cells.
- "**Magic bullet**" drug, is a dream that did not materialize yet.

➢ Toxicity of Cancer Chemotherapy

1. Cells of the bone marrow, the lymphatic system, and the lining of the intestinal tract are very sensitive to cytotoxic drug effects.
2. Almost all anticancer drugs cause toxicity, e.g.:
    a) Bone marrow suppression: Nitrogen mustard.
    b) Immunosuppression: Methotrexate.
    c) Neuropathy: Vincristine.
    d) Cardiotoxicity: Doxorubicin (Adriamycin)

➢ Special Problems/Practical Points of anti-cancer drugs

1. Need special storage strategies.
2. Preparation
3. Administration techniques
4. Extravasation of injection:
   (IV administration causes vasculitis and irritation of blood vessels)
5. oral administration results in vomiting

- so we combine them with other drugs to decrease this effect, like:
    a) **Lorazepam** (for anxiety)
    b) **Dexamethasone**, **Domperidone**
    c) **Ondansetron** -5HT3 antagonist- (for vomiting)

6. Teratogenesis.
7. Bone Marrow suppression.
8. Immunosuppression leading to severe infections.

➢ Relative Chemosensitivity of Tumors

Highly Sensitive tumors (May be cured by chemotherapy**)**	**Moderately Sensitive tumors:** (Chemotherapy may sometimes contribute to cure and often palliates)	**Relatively Insensitive tumors:** (Chemotherapy may sometimes produce palliation)	**Resistant Tumors:** (no improvement by chemotherapy)
Examples: - Teratoma of Testis (you don't need to remove the tumor only chemotherapy) - Hodgkin's + high-grade non- Hodgkin's Lymphomas - Wilms's Tumor - Embryonal Rhabdomyosarcoma - Choriocarcinoma - Acute Lymphoblastic Leukemia in children - Ewing's Sarcoma	**Examples**: - Small cell carcinoma of the lung - Breast carcinoma - Low grade non-Hodgkin's Lymphoma - Acute Myeloid Leukemia - Ovarian cancer - Myeloma	**Examples:** - Gastric carcinoma - Bladder carcinoma - Squamous cell carcinoma of head and neck - Soft tissue sarcoma - Cervical carcinoma	**Examples:** - Melanoma - Squamous cell carcinoma of the lung - Large bowel cancer

The doctor said "you don't need to memorize all these examples"

➢ Resistance to Cytotoxic Drugs:

1. **Primary or Inherent Resistance**: Absence of response on the first exposure, and they should not be treated with chemotherapy.
   (e.g.: - Melanoma, renal cell carcinoma, brain cancer).
2. **Acquired Resistance**: the tumor is sensitive to chemotherapy at the beginning of treatment then suddenly the tumor cells develop resistance to chemotherapy.
   A. **Highly Specific**: the tumor cells develop resistance for **one single drug**. This resistance is based on a change in the genetic apparatus of a given tumor cell with amplification or increased expression (gene amplification) of one or more specific genes (mutation in tumor cells).
   B. **Multidrug-Resistance (Pleiotropic متعدد الاتجاهات):**
   - Resistance to a variety of natural product anticancer agents of different structures developing after exposure to a single agent.

- Associated with increased expression of a normal gene (the MDR1 gene) for a cell surface glycoprotein (P-glycoprotein) involved in drug efflux.
- this glycoprotein requires ATP to expel a variety of foreign molecules and not limited to anticancer drugs (remember the same protein used by certain bacteria to develop resistance to antibiotics).
- Reversed by calcium channel blockers; they help in treatment of cancer.
- Could also be due to overexpression of the multidrug resistance protein1 (MRP1), which can function as a drug export pump.

C. Biochemical Resistance:

Decreased drug transport into the cells, or alteration in the structure of the target enzyme, or changes in cell DNA repair capability.

➢ Complications of Chemotherapy:

Immediate Complications: (appears after second or first week of treatment)	**Long term complications:**	
-Nausea and vomiting. -Mucosal ulcerations. -Bone marrow depression. -Alopecia.	-Infertility -Pulmonary fibrosis -Nerve damage -Renal impairment	-Secondary cancers - Cardiomyopathy -Loss of hearing

➢ Cell Cycle:

- Cells, normal and cancerous, pass through a series of phases during their life.
- Cancer cells in G0, will be in the resting phase, and they will be least sensitive to chemotherapy.
- Cytotoxic drugs interfere with DNA or RNA and thus have profound effects on normal cells (mainly rapidly dividing cells) and malignant cells.

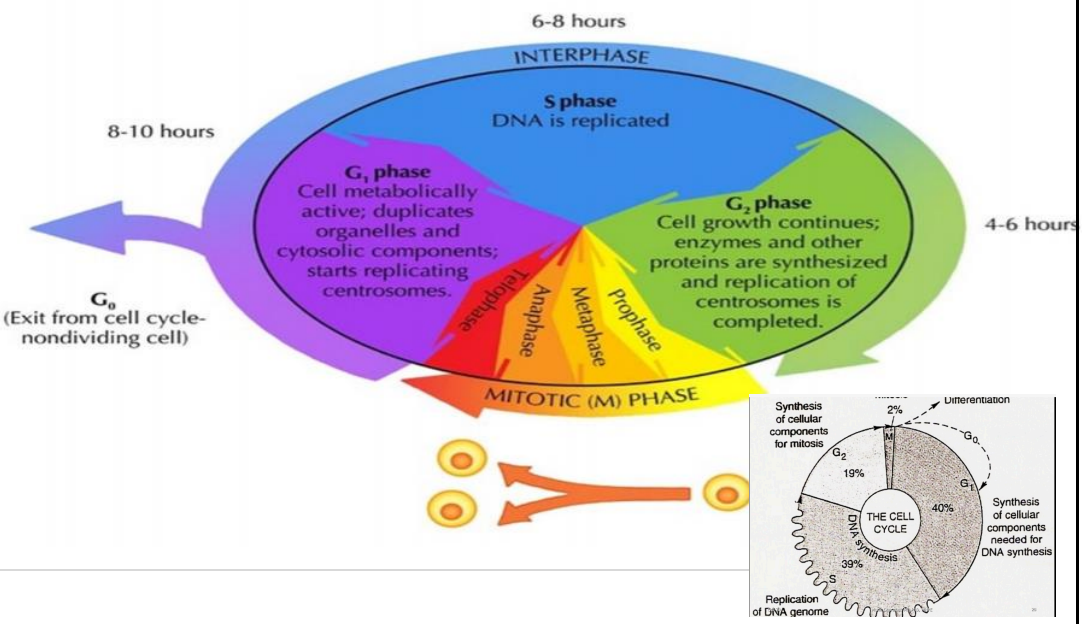
G0: Resting phase.

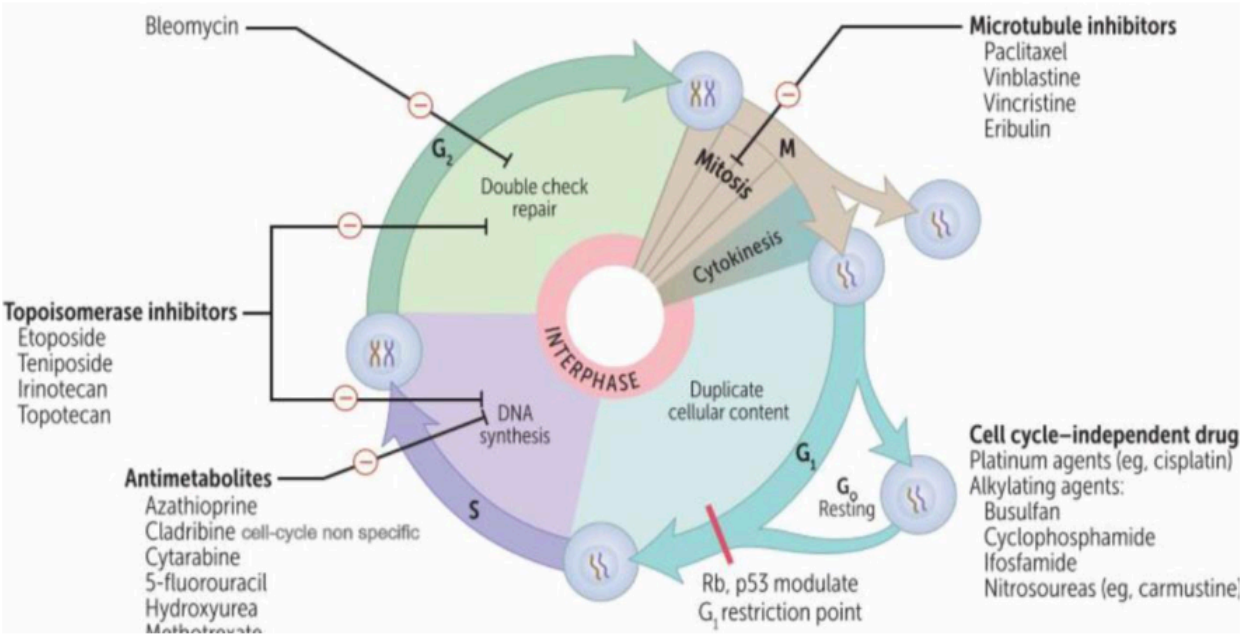
G1: Initial phase, enzyme synthesis.

S: DNA synthesis.

G2: Synthesis of cellular components required for mitosis.

M: Mitosis, Cell division phase.

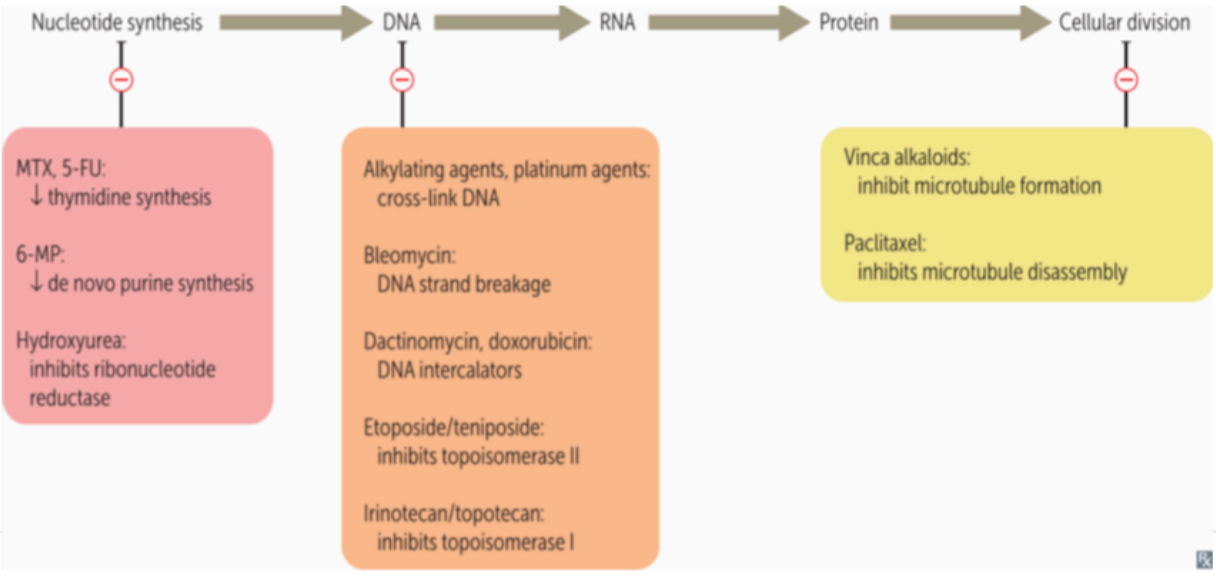




Anti cancer drugs :

1-Nucleotide synthesis / 2- DNA synthesis / 3- RNA synthesis / 4- Protein synthesis

5- Cellular division process



I. cell cycle–specific (CCS) drugs:

- effective anticancer drugs; they exert their action on cells traversing the cell cycle.
- Effective only when a large proportion of cells is proliferating or in the growth fraction.

Antimetabolites	Antitumor Antibiotics	Epipodophyllotoxins	Taxanes	Vinca Alkaloids
- Capecitabine - Cladribine - Cytarabine - Fludarabine - 5-Fluorouracil(5-FU) - Gemcitabine - 6-Mercaptopurine(6-MP) - Methotrexate - 6-Thioguanine(6-TG)	- Bleomycin	- Etoposide - Teniposide	- Docetaxil - Paclitaxil	- Vinblastine - Vincristine - Venorelbin

We are not required to memorize all these examples

II. Cell cycle– nonspecific (CCNS) drugs:

- they can kill tumor cells whether they are cycling or resting in the G0 compartment. CCNS drugs can kill both G0 and cycling cells (although cycling cells are more sensitive), so **CCNS more effective than CCS.**
- Can sterilize tumor cells whether they are cycling or resting in the G0 compartment, they can kill cancer cells even if they are slowly multiplying.
- Useful both in low growth fraction solid tumors as well as in high growth fraction tumors.
- Bind to cellular DNA and damage these macromolecules.

Alkylating Agents	Anthracyclines	Antitumor Antibiotics	Camptothecins	Platinum Compounds
- Busulfan - Carmustine - Cyclophsphamide - Lomustine - Mechlorethamine - Melphalan -Thiotepa	- Daunorubicin - Doxorubicin - Epirubicin - Idarubicin - Mitoxantrone	- Dactinomycin - Mitomycin	- Irinotecan - Topotecan	- Carboplatin - Cisplatin - Oxaliplatin

We are not required to memorize all these examples

Good luck