Athar Batch

Pharmacology

Lecture: 37+38

Done By : Toleen Alkasaji

النادي الطبي

Chemotherapy for Neoplastic Diseases

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

Tareq Saleh, MD, PhD

Faculty of Medicine

The Hashemite University

Cancer is thought to be a new disease that has developed over the last 200 years due to environmental changes.
* unhealthy diet.
* Smoking.
* Air pollution.

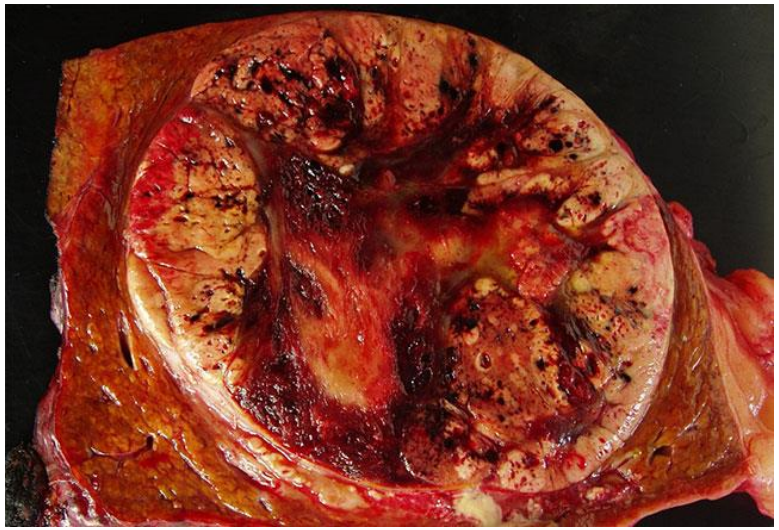
but cancer is an old disease that had been since humans had been there.

History of Cancer

- The earliest reference to cancer goes back to ancient Egypt (3000 BC). Those cases of cancer were treated by cauterization. الكي
- The word "cancer" (which means crab) was described by Hippocrates (460-370 BC) because of the invasive projections of cancer in the adjacent tissue.
- Later, the Greek root "oncos" (which means swelling) was used to describe tumors.
- Giovanni Morgagni identified and described cancers by performing autopsies (1761); John Hunter (1728-1793) proposed surgical removal of tumors.

oncology and oncologist is the doctor that is responsible for the diagnosis and the managment of cancer.

using surgery for the treatment of cancer was the first model of cancer treatment and is still a main state of treatment to many solid tumors.



Liver Cancer, Image courtesy of Arief Suriawinata, MD, Department of Pathology, Dartmouth Medical School

American Cancer Association

Cancer Statistics

Most Common

the deadliest type of cancer in both the males and females is the lung cancer.

* very aggresive.
* very malignant.
* very difficult to treat.

Least Common

the most frequently diagnosed cancer is the prostate cancer.

the most common type of cancer.

Estimated New Cases

Males			Females		
Prostate	248,530	26%	Breast	281,550	30%
Lung & bronchus	119,100	12%	Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%	Colon & rectum	69,980	8%
Urinary bladder	64,280	7%	Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%	Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%	Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%	Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%	Pancreas	28,480	3%
Leukemia	35,530	4%	Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%	Leukemia	25,560	3%
All Sites	**970,250**	**100%**	**All Sites**	**927,910**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	69,410	22%	Lung & bronchus	62,470	22%
Prostate	34,130	11%	Breast	43,600	15%
Colon & rectum	28,520	9%	Colon & rectum	24,460	8%
Pancreas	25,270	8%	Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%	Ovary	22,950	5%
Leukemia	13,900	4%	Uterine corpus	12,940	4%
Esophagus	12,410	4%	Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%	Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%	Brain & other nervous system	8,100	3%
All Sites	**319,420**	**100%**	**All Sites**	**289,150**	**100%**

Cancer isn't a single disease but it's a spectrum of diseases depending on the type or tissue of origin.

- Cancer is the second leading cause of death in the US.
- >25% of the US population will be diagnosed with a type of cancer during their lifetime.
- In 2021, 1,898,160 new cancer cases and 608,570 cancer deaths are projected to occur in the United States

Siegel et al, 2021

Surgical methods followed by radiation were used respectively to treat cancer.

History of Chemotherapy

derivatives of NMCs are now used in the treatment.

Nitrogen Mustard Compounds were biological weapons that were used in WWII.

they were effective against leukemia.

this was the beginning of thinking that some drugs can be effective in eleminating tumor cells.

he treated children with leukemia.

- During WWII, *nitrogen mustard* was developed, and found to work against *lymphoma* (studies by Goodman and Gilman).
- Sidney Farber studied *aminopterin*, which interferes with folic acid metabolism necessary for DNA replication.

cancer cells are very dependant on folic acids for their growth and proliferation.

- After Farber, the era of chemotherapy has begun.
- About a quarter of cancer patients will be cured solely by *surgery*.
- Most cancer patients will receive systemic *chemotherapy* and only 10% will be cured or have a prolonged remission.

Sidney Farber, Boston, MA

History of Chemotherapy

the children had temporary responses to the chemotherapy and then higher number of children had relapse and the cancer got back again to them.

"Cancer Can Be Treated With Drugs Of Chemotherapy".

SOME OBSERVATIONS ON THE EFFECT OF FOLIC ACID ANTAGONISTS ON ACUTE LEUKEMIA AND OTHER FORMS OF INCURABLE CANCER

By Sidney Farber, M.D.

THE PRODUCTION of temporary remissions in the course of acute leukemia in children by the administration of the compound, 4-aminopteroylglutamic acid (aminopterin)[1,2]—a biologic antagonist to folic acid*—has raised a number of theoretic and practical questions. Confirmation of this finding has been reported from several sources[3]; temporary remissions equally impressive have been obtained in adults with acute leukemia by Dameshek.[4]

It is the purpose of this paper to summarize briefly the status of our observations† on the action of folic acid antagonists on acute leukemia and other incurable forms of cancer for the interest of those now working with these agents, to state the nature of some of the problems which have arisen, and to indicate some directions of further research.

The demonstration by Lewisohn and his colleagues[5] of the occurrence of complete regression in about one-third of single spontaneous breast cancers in three different strains of mice treated with fermentation L. casei factor, later shown to be pteroyltriglutamic acid (Hutchings et al.[6]) and the subsequent synthesis of this compound by SubbaRow and his co-workers[7] led to our study of the effect of pteroyltriglutamic acid on incurable cancer in man. Among the patients so treated were 11 children with acute leukemia. The occurrence of what we called an "acceleration phenomenon" in the viscera and bone marrow of these patients and an experience with folic acid deficiency experimentally produced in the rat suggested that it would be worth while to ascertain if this acceleration phenomenon might be employed to advantage in the treatment of acute leukemia in children, either by the use of radiation or nitrogen mustard therapy after pretreatment with folic acid or conjugates of folic acid, or by the immediate use of folic acid inhibitors or

Hallmarks of Cancer

Cancer is defined in the simplest terms as an abnormal or uncontrolled proliferation and an uncontrolled growth of the cells.

Human/mammalian cells are daily growing and dividing like in the skin / Bone marrow but they all grow and die in a concentrate in a very well balanced pattern and they can respond to growth stimuli and grow and they can respond to antigrowth signals and stop growing.

Cancer cells should have a certain set of hallmarks that make the cancer special against any other abnormal growth.

Self-sufficiency in growth signals — independant on the growth stimulation and they grow on their own.

Evading apoptosis — have a bigger ability to survive apoptosis and any other regulating stimuli.

Insensitivity to anti-growth signals — they stop being sensitive to anti-growing signals.

their job is to keep tissue proliferation in balance.

Sustained angiogenesis — they have the ability to promote their own blood supply to maintain their own nutrients.

Tissue invasion & metastasis — having the ability to move from the primary site of cancer tumor and disseminate through the lymphatic vessels, blood vessels to a different site in the body.

Limitless replicative potential — uncontrolled growth of cells.

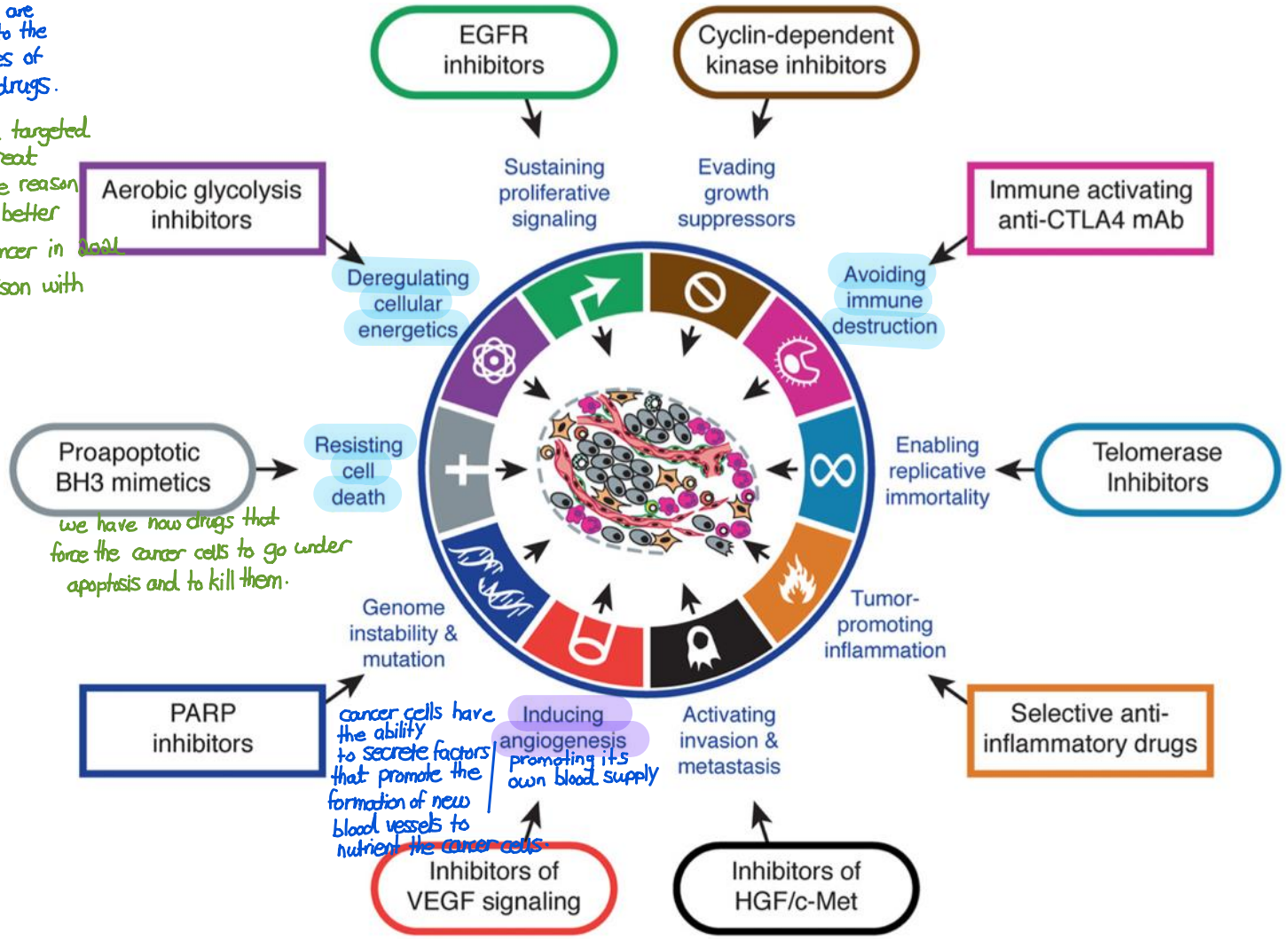
is only related to malignant tumors because benign tumors don't have the ability to metastasize.

Hanahan and Weinberg, 2000

Hallmarks of Cancer

those features are now targets to the newer classes of anticancer drugs.

very new effective targeted modalities to treat cancer are the reason why we have better treatment to cancer in 2021 with comparison with WW II.



we have now drugs that force the cancer cells to go under apoptosis and to kill them.

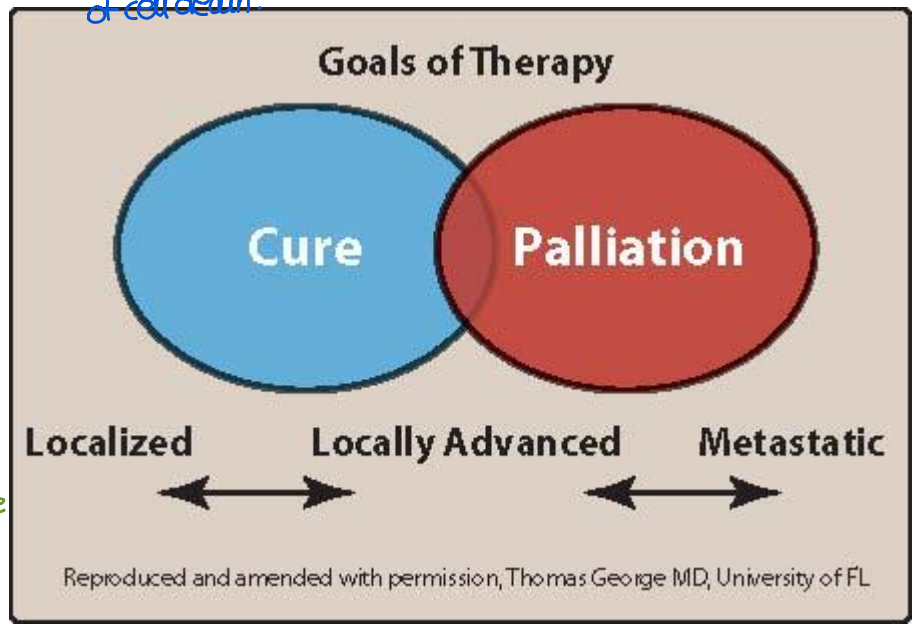
cancer cells have the ability to secrete factors that promote the formation of new blood vessels to nutrient the cancer cells promoting its own blood supply

Hanahan and Weinberg, 2011

Principles of Antineoplastic Chemotherapy

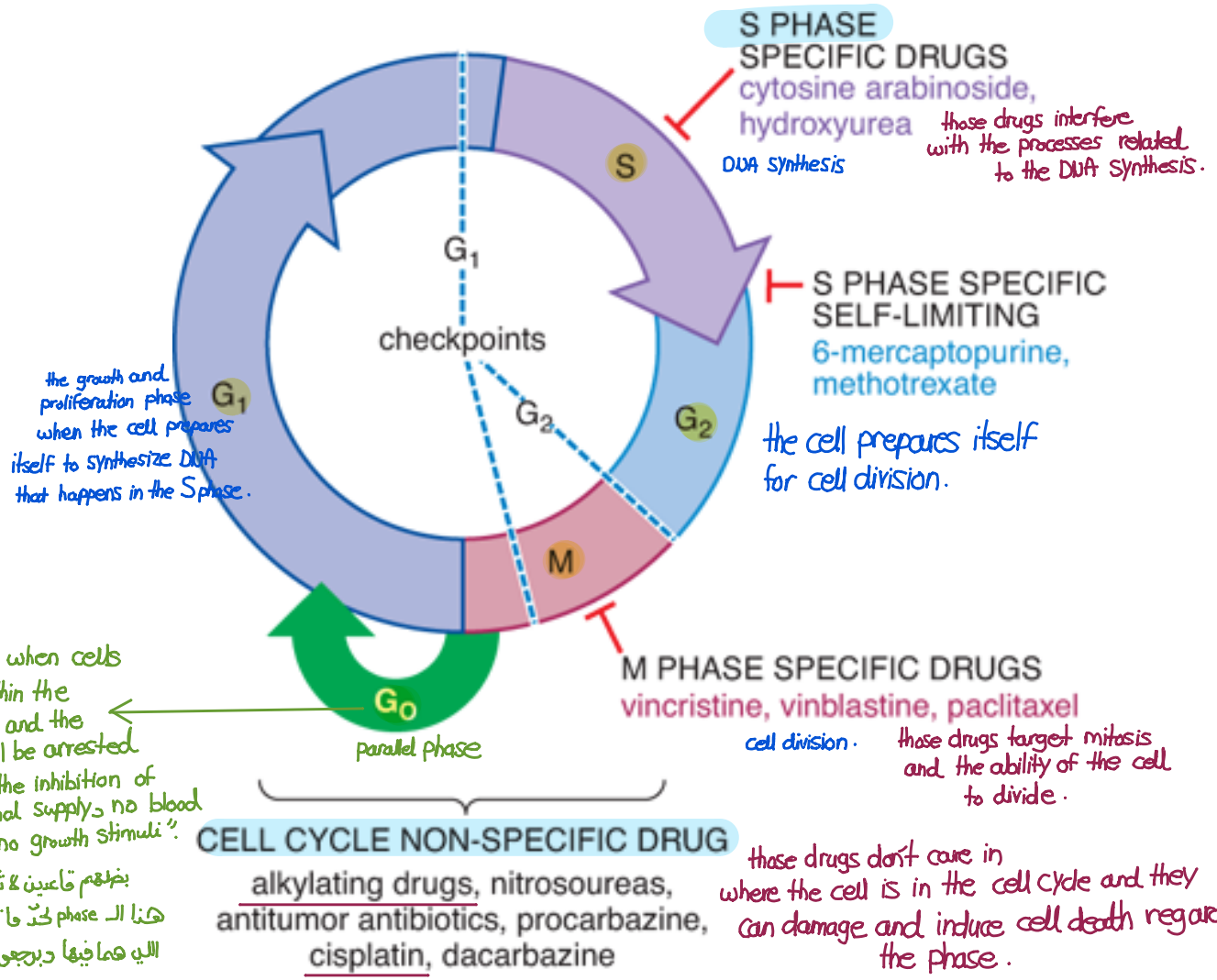
- **Main goal**: to induce cell death/growth arrest (apoptosis, necroptosis, senescence, cytotoxic autophagy, mitotic catastrophe….) in tumor cells.
  - Cure, long-term, disease-free survival
  - Debulking, treating cancer as a chronic disease
  - Palliative treatment
- Selective toxicity?
- Recent therapies aim at utilizing the immune system in eliminating tumor cells.

became a programmed cell death
"an alternative mode of regulated cell death mimicking features of apoptosis and necrosis".
the new name of necrosis
inducing multiple types of cell death



by eleminating the majority of cancer cells.
reducing the size of the cancer/tumor and killing a part of those cells.
"allowing better surgical access"
in the case of advanced stages of cancer
curing symptoms related to cancer in the existence of the tumor.
مثلاً بعض حجم فيبطل ضاغط على العصب أو مثلاً مسكر مجرى جزء من الأمعاء وهكذا.
we're targeting human cells, so the selective toxicity is very low because we're targeting normal, non-cancerous cells as were treating cancer cells.

Understanding the cell cycle



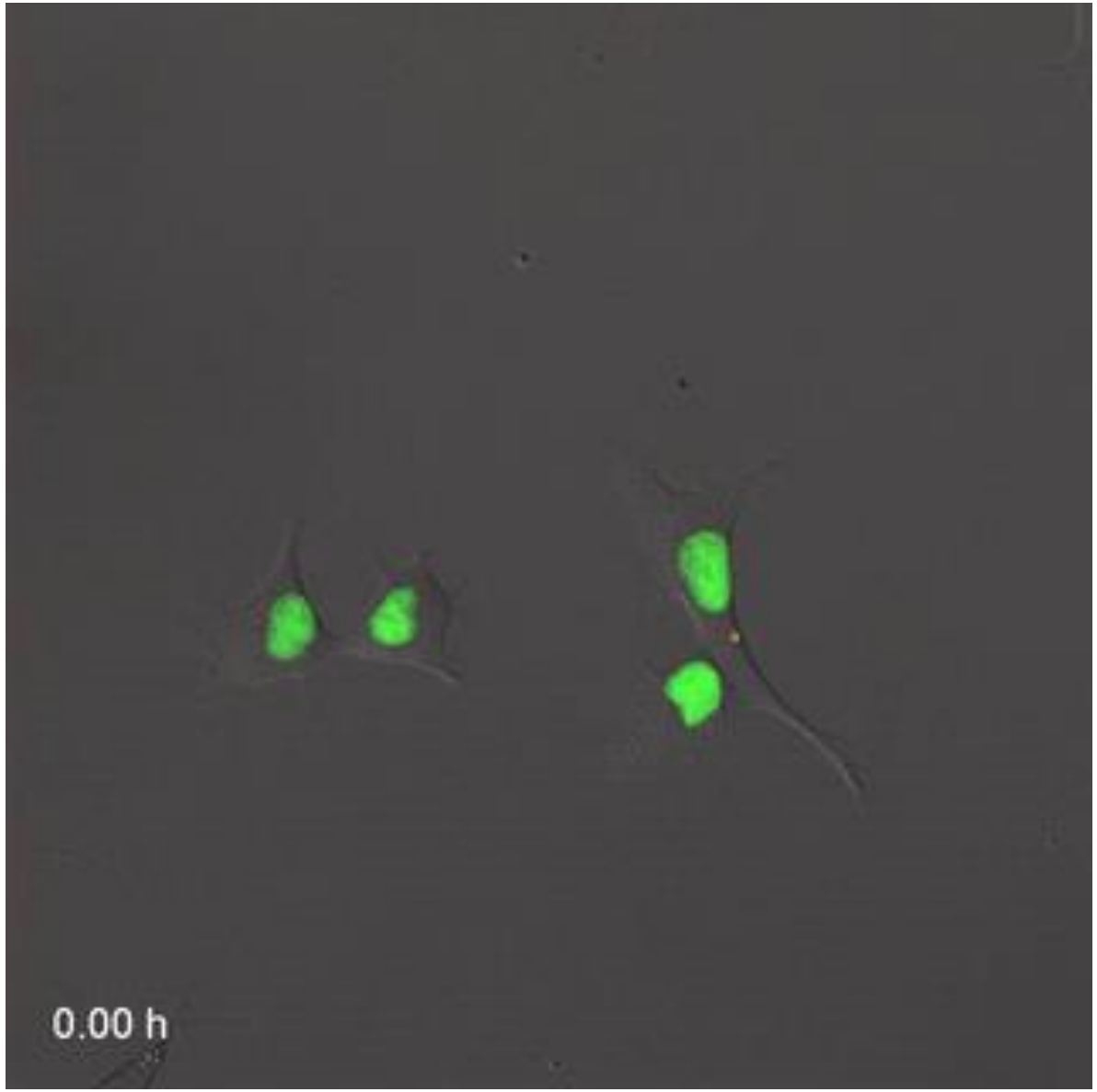
- Neoplasms with high percentage of proliferation are, most susceptible to cycle-specific therapy

tumors with high growth rate are more susciptable for cell cycle specific therapy like luekemia because they grow and proliferate more thus going through the cell cycle more and more.
" liquid cancers/tumors".

- Slow growing tumors e.g., CRC, NSCLC are less responsive to cycle-specific drugs

less in the rate of the proliferation growth.
colorectal cancer
Non-Small cell lung cancer
+ lung cancer
those are solid tumors and they cause masses.

Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com



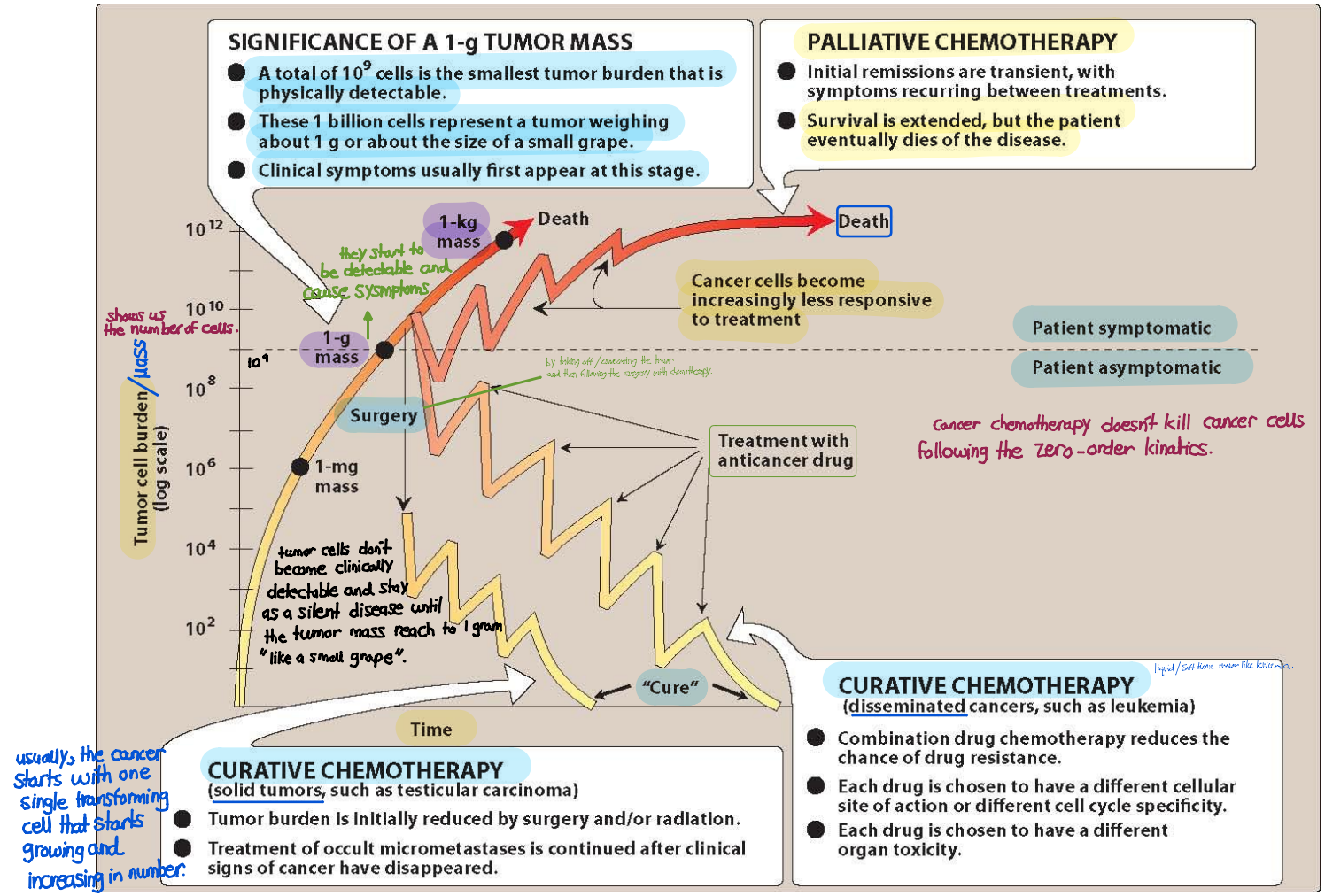
By Erin Rod - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=50866822

Log-kill phenomenon

- Destruction of cancer cells by chemotherapeutic agents follows **first-order kinetics** *OR* **log kill phenomenon.**

A given dose of drug destroys a constant fraction of cells

* the chemotherapy is given in cycles.



Log-kill phenomenon

- Example: Diagnosis of leukemia is made at 10^9 leukemic cells
- If treatment results in 99.999% killing → 0.001% remain
- This is equal to log kill 5
- State of remission (asymptomatic)
- Comparison with antibiotics?

بتقتل بنسبة ثابتة

Cell Fraction Killed	Surviving Cell Fraction	Log Surviving Cell Fraction	Log Kill
.9	.1	-1	1
.99	.01	-2	2
.999	.001	-3	3
.999999999	.000000001	-9	9

بتقتل ٩٠٪ من الـ ١٠٪

the state of remission. حالة الشفاء

Chemotherapy: anticancer vs. antimicrobial

they're very toxic drugs.

- **Selective Toxicity** so they get targeted without the human/mammalian cells.

-Biological processes (DNA synthesis, protein synthesis, metabolism, etc) in bacteria, fungi, parasites, etc are essentially different from host cells.

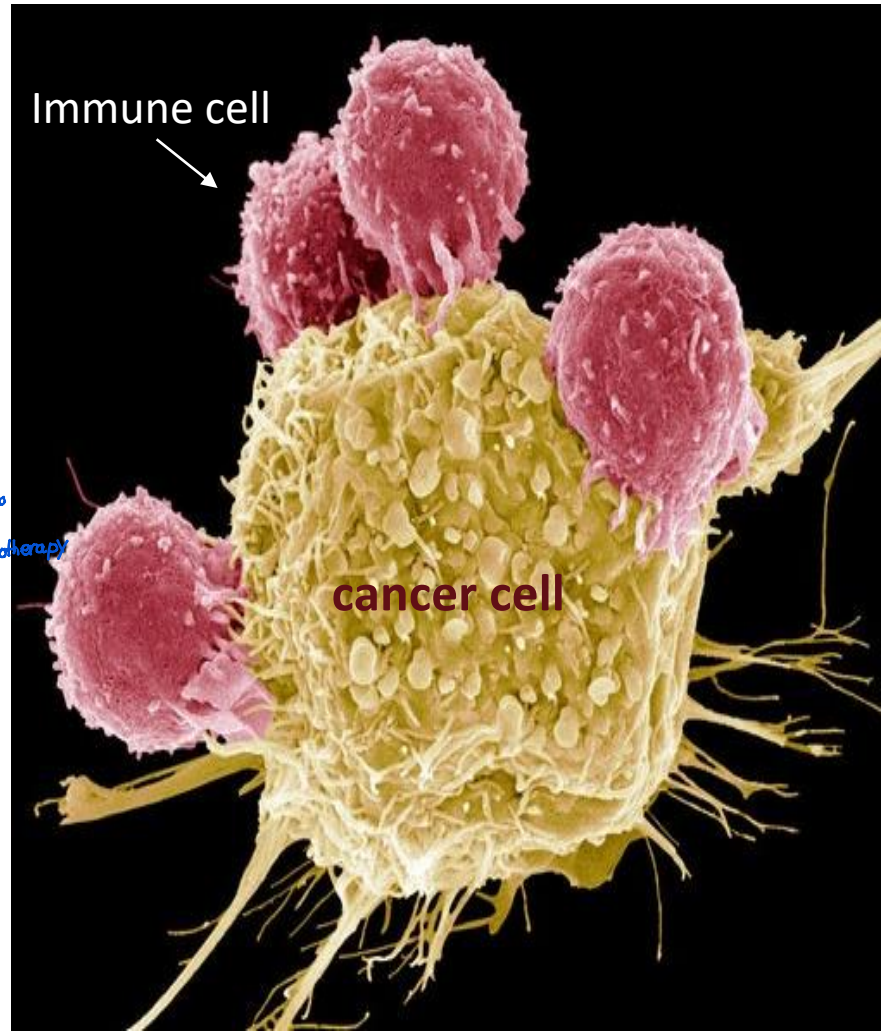
-Cancer cells are transformed host cells and their metabolic processes are similar (only altered). so if we target a process in a tumor we'll also target the same process in the normal and non-cancerous cells, so the selective toxicity of chemotherapy is very low.

- **Immune system**

-The host immune system targets and eliminates invading, foreign microorganisms. the immune system won't always help us in detecting the cancerous cells.

- **Diagnostic Complexity**

- Cancer early detection and diagnosis is challenging. the diagnosis of cancer is more complicated and may have late treatment unlike the clear and fast diagnosis of infections.

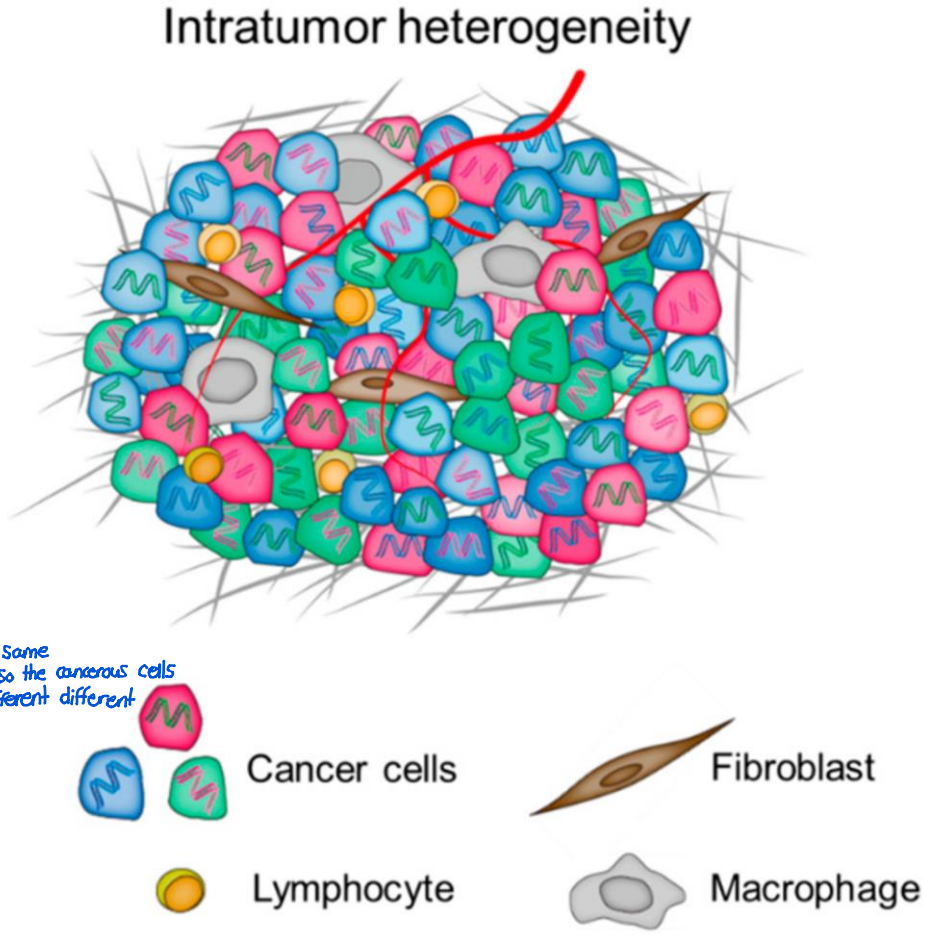


Treatment Protocols

Combination Chemotherapy

- Chemotherapies with different mechanisms of action are usually combined
  usually the set contains 3-5 anticancer drugs or even more.
- More successful than monotherapy
  - ❖ Additive/synergistic effects – maximal cell killing
  - ❖ Covers broader range of cell lines (heterogeneous tumor population)
    the cancerous cells in the same tumor aren't the same, so the cancerous cells in the same tumor have different different features
  - ❖ Delay resistance
    the resistance to chemotherapy is fast.
  - ❖ Non-overlapping host toxicities (different adverse effects)
    by choosing multiple drugs with different mechanisms of action. so spare certain organs from being completely damaged.

So we use multiple agents to besiege the different types of cancer cells.



Resistance Against Antineoplastic Chemotherapy

- **Inherent resistance**
  - e.g., melanoma cells

Skin cancer.

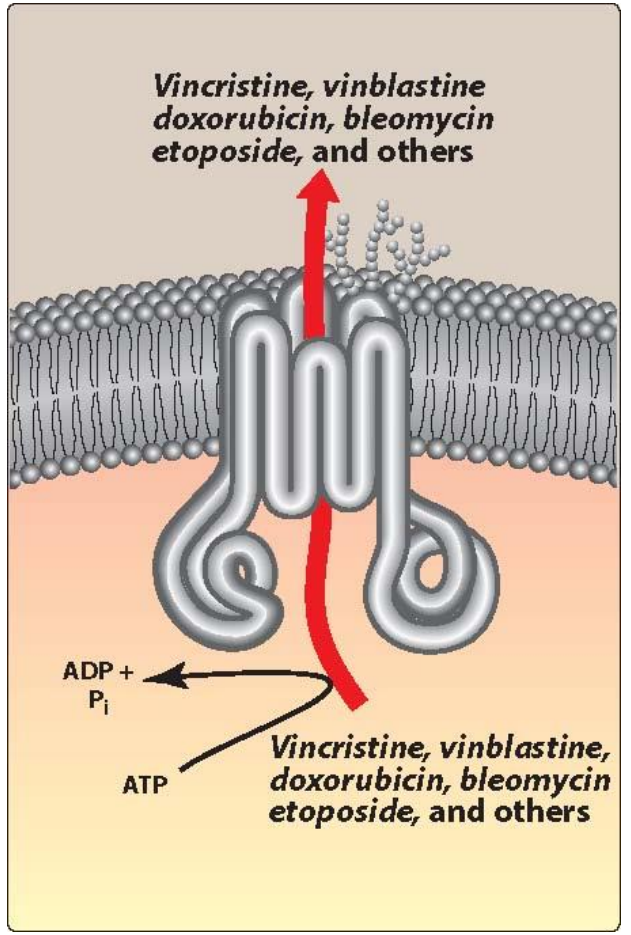
- **Acquired resistance**

most of the cancer types acquire resistance after the exposure to drugs/chemotherapy.

  - Several mechanisms:
    1. P-glycoprotein efflux pump (multi-drug)

its function is effluxing the anticancer drug out the cancerous cells.

    2. Specific to antineoplastic agent
  - After prolonged administration of suboptimal doses



transmembrane pump

How is Antineoplastic Given?

- **Adjuvant chemotherapy:**
  - Chemotherapy given after surgery or irradiation to destroy micrometastasis & prevent development of secondary neoplasm.

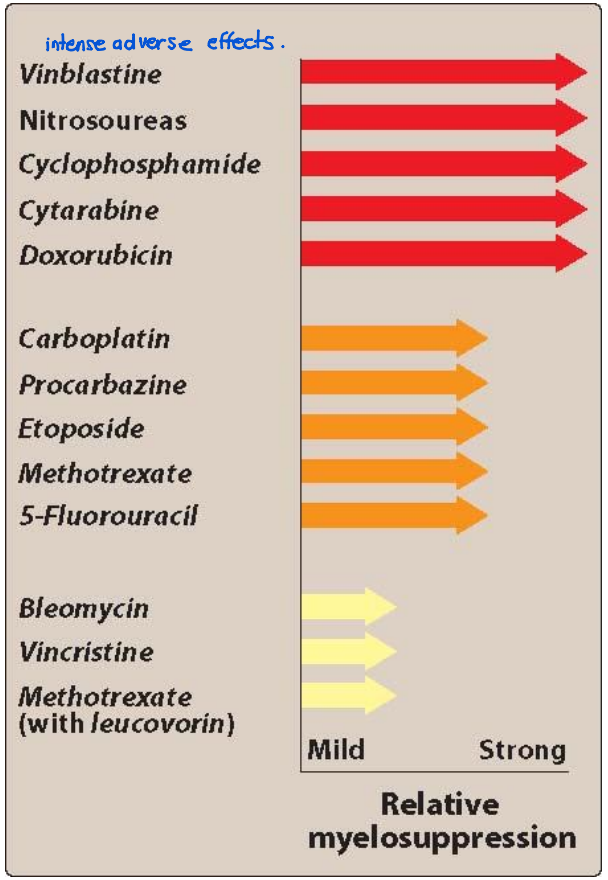
After the eradication of the tumor/cancerous mass surgically then the chemotherapy is given to destroy the remnants of the tumor in addition to the micrometastasis.

- **Neo-adjuvant chemotherapy:**
  - Chemotherapy given before surgery or radiotherapy in order to diminish the volume of large primary neoplasm

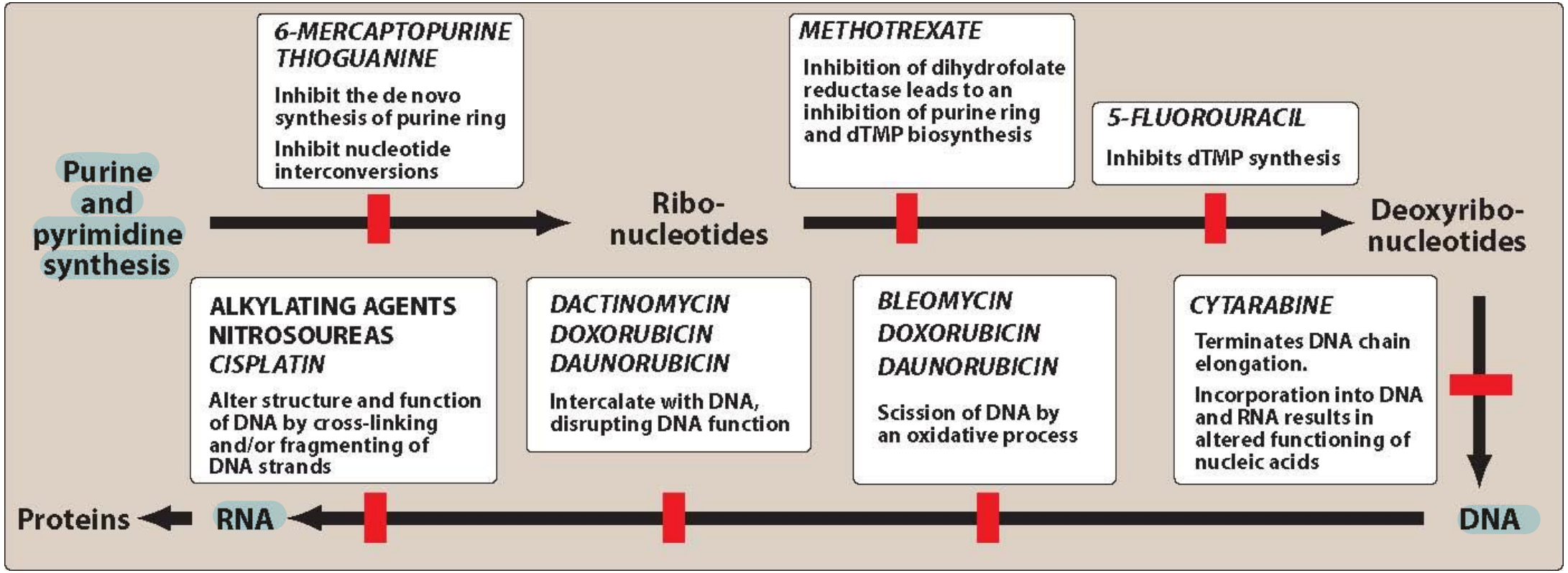
to debulk the tumor mass helping in its surgical eradication and enhancing the outcome of the chemotherapy.

Adverse Effects of Antineoplastic Chemotherapy

- Rapidly proliferating non-tumor cells are most susceptible:
  - ❑ Buccal mucosal cells, bone marrow, gastrointestinal mucosa, hair follicles…)
- **Examples:** very common between most types of chemotherapy.
  - ➢ Chemotherapy-Induced Nausea/Vomiting
  - ➢ Alopecia the absence of the hair. because hair follicles are rapidly proliferating so they will be susciptable to the chemotherapy then die.
  - ➢ Bone Marrow Suppression
  - ➢ Chemotherapy-Induced Peripheral Neuropathy
  - ➢ Carcinogenesis the process by which normal cells are transformed into cancer cells.
  - ➢ Hypogonadism infertility.
  - ➢ Teratogenicity
  - ➢ Organ-specific Adverse Effects



Most Common Conventional Chemotherapy

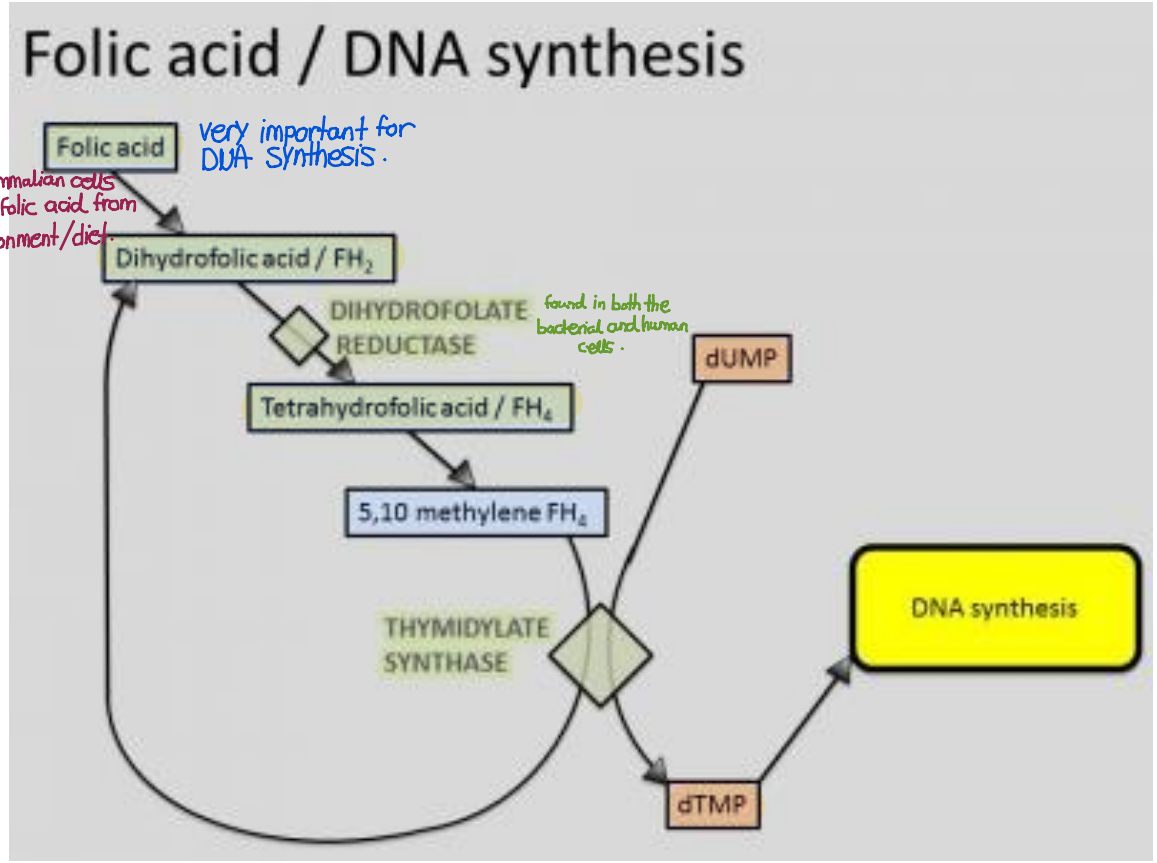


Antimetabolites

Antimetabolites

those will interfere with the human cancer processes.

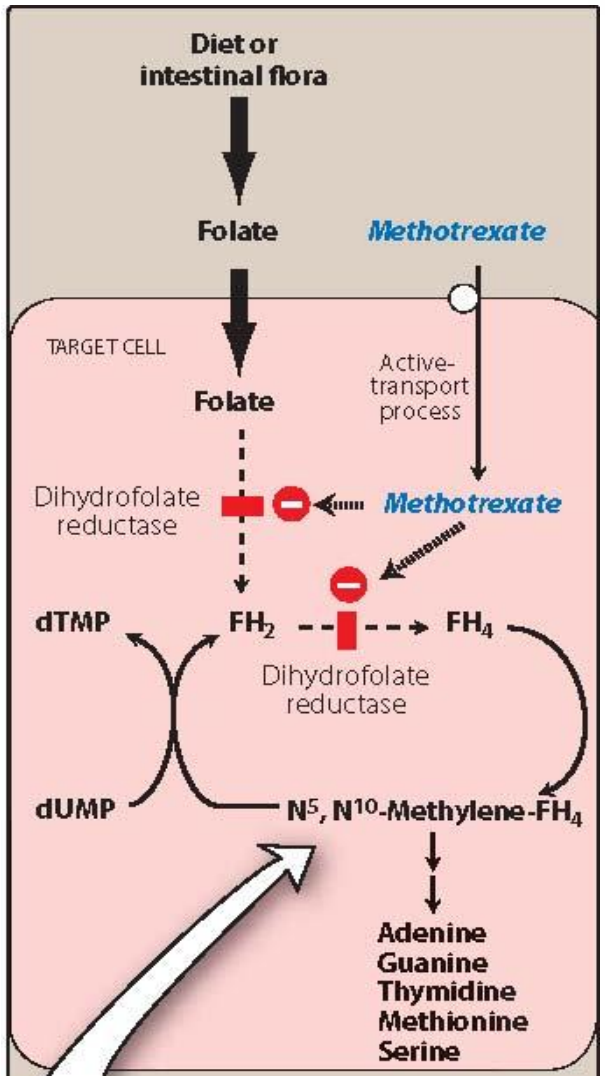
Folic acid plays a pivotal role in purine and thymidylate synthesis involving the transfer of one-carbon units, thus, is essential for cell replication



Methotrexate and pemetrexed

- *Methotrexate* is structurally related to folic acid
- **Mechanism of action:** INHIBITS MAMMALIAN DIHYDROFOLATE REDUCTASE (DHFR) thus inhibits folic acid synthesis then DNA synthesis. preventing the cancer cells from growing
- **Cell cycle specific:** S phase

Pemetrexed inhibits DHFR and thymidylate



Methotrexate

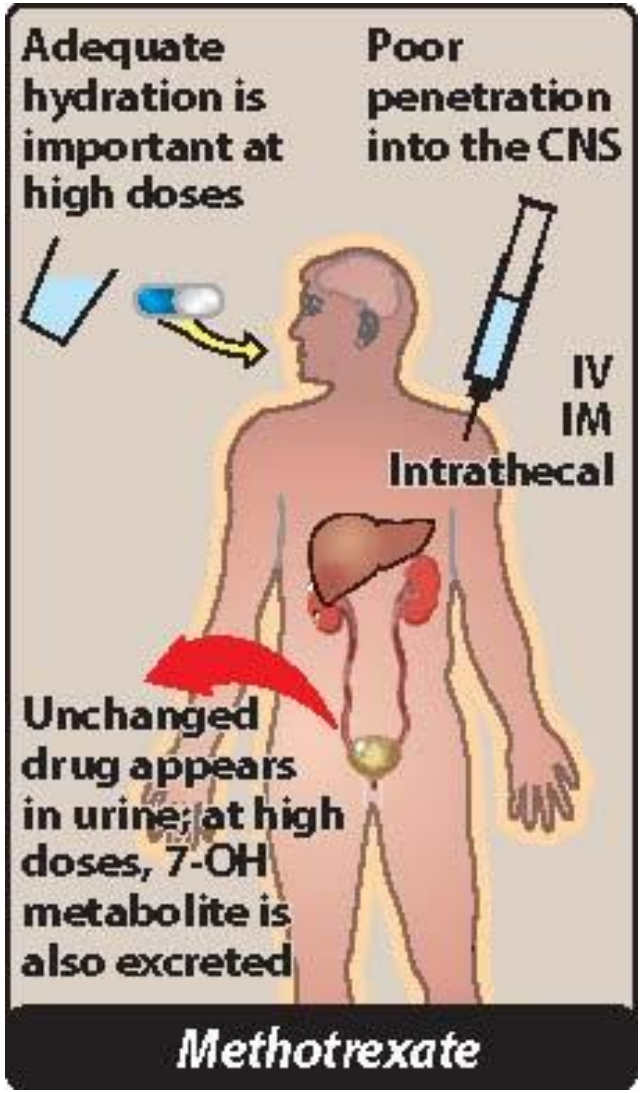
- **Therapeutic uses (methotrexate):**

(in combination with other chemotherapies)

1. Acute lymphocytic leukemia
2. Burkitt lymphoma
3. Other cancers (breast, bladder and head and neck cancers ….)
4. Autoimmune diseases e.g., rheumatoid arthritis, Crohn's disease

Methotrexate

- Oral, IM, IV, intrathecal if the leukemia goes to the CNS.
- Poor penetrance across the BBB عشان أحاصر الخلايا السرطانية جوّا الـ CNS.
- Metabolism: MTX undergo hydroxylation at 7th position to form 7-hydroxymethotrexate (less water soluble)
- Excretion of metabolites in urine



Methotrexate

- **Adverse effects:**

❑N/V/D

❑Cutaneous reactions/rash

❑Alopecia especially in young children.

❑Myelosuppression bone marrow toxicity

❑Renal damage

❑Neurologic toxicities (if given intrathecally)

Reason for discontinuation	Discontinued methotrexate permanently (n)	Per cent of discontinuations (n = 46)	Per cent of all patients (n = 248)
Adverse effects	26	56.5%	10.4%
Gastrointestinal	6	13.0%	2.4%
Oral ulcers	3	6.5%	1.2%
Skin rash	3	6.5%	1.2%
Malaise	3	6.5%	1.2%
Pulmonary symptoms	3	6.5%	1.2%
Pneumonia	2	4.3%	0.8%
Nodules	2	4.3%	0.8%
Laboratory abnormalities	2	4.3%	0.8%
Other side effects	2	4.3%	0.8%
Inefficacy	15	32.6%	6.0%
Other reasons	5	10.9%	2.0%
Disease improved	3	6.5%	1.2%
Other diseases	1	2.2%	0.4%
Pregnancy	1	2.2%	0.4%

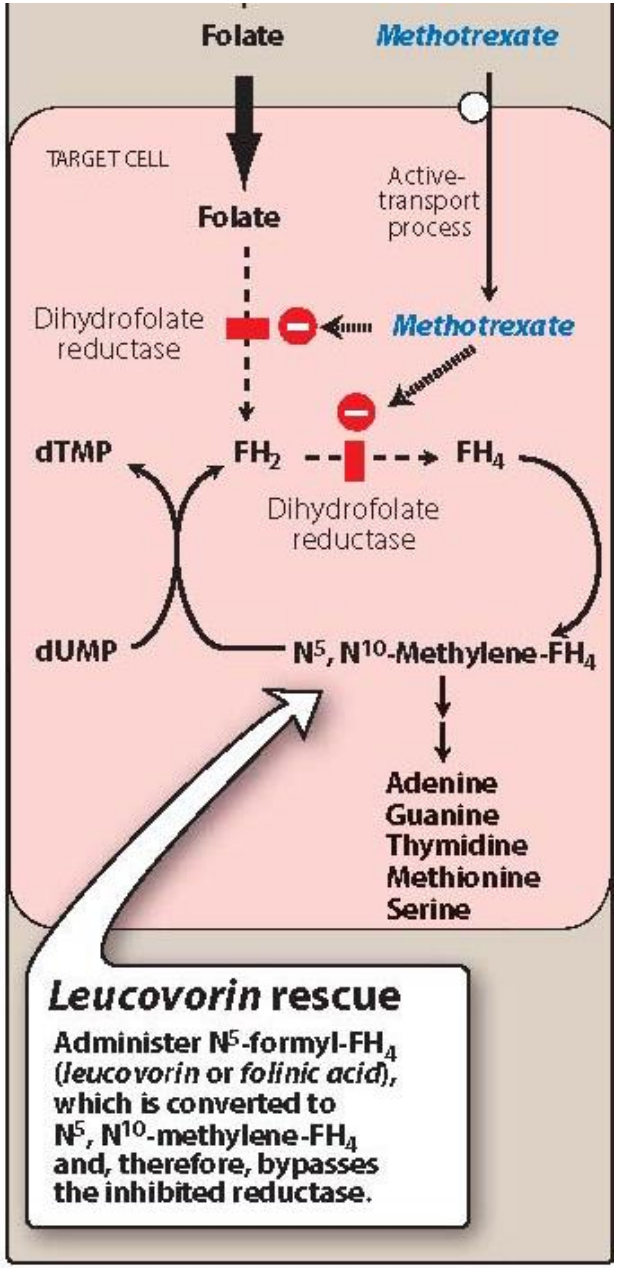
How to overcome the adverse effects of methotrexate?

A. Always administer with folic acid and vitamin B_{12} (to reduce GI/hematologic side effects)
B. Pretreatment with corticosteroids (to reduce cutaneous reactions)
C. Leucovorin folic acid

Leucovorin

- Leucovorin (folinic acid) is *tetrahydro* derivative of folic acid used to rescue normal, proliferating cells from the effects of methotrexate.

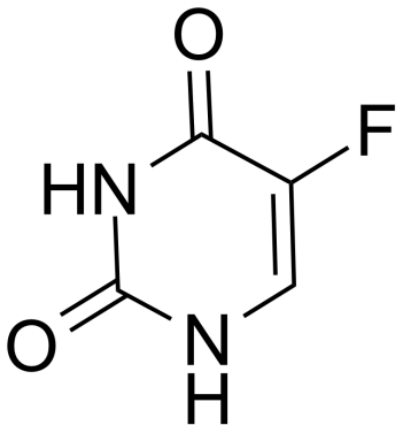
- Leucovorin is usually administered 24 hours after methotrexate so that it does not interfere with the therapeutic effect of methotrexate.



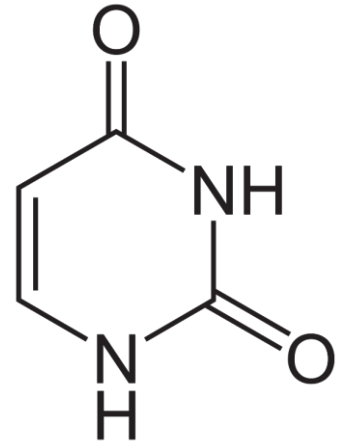
5-Fluorouracil

- Pyrimidine analog
- **Therapeutic Uses**

1. Slow-growing solid tumors. e.g. colorectal, breast, gastric cancers….
2. Topically for superficial basal cell carcinoma



5-Fluorouracil

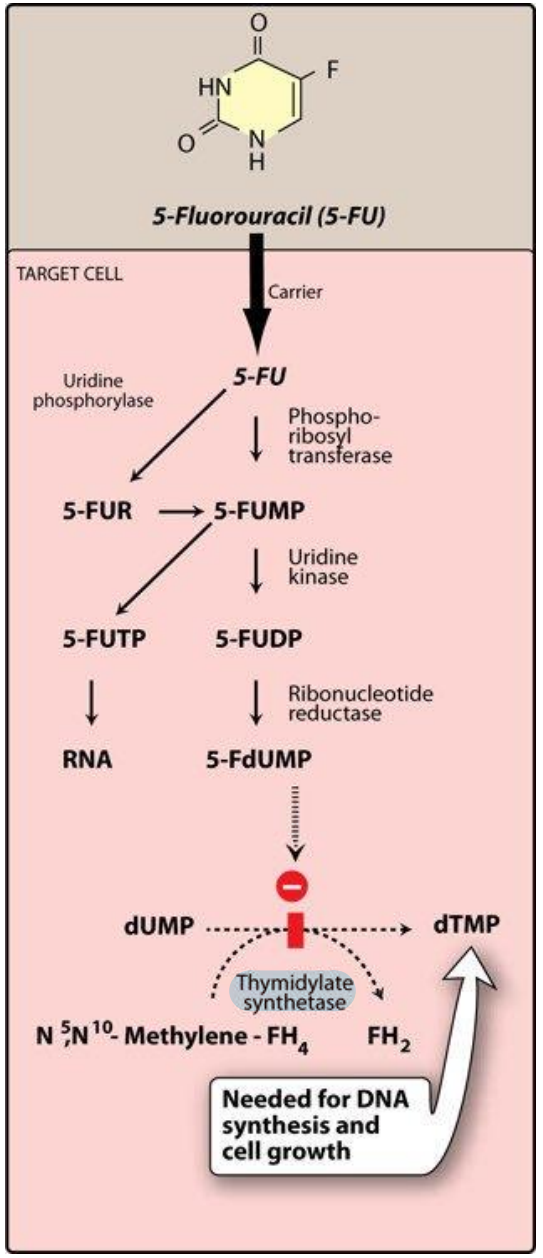


Uracil

5-Fluorouracil

Mechanism of action

- 5-FU itself has no antitumor effect
- Enters tumor cells through carrier-mediated transport system
- Converted to 5-FdUMP
- Inhibits thymidylate synthase



Microtubule Inhibitors

"Slides are enough for this lecture"