Artery Academy

Done By Mariam Yacoub

هاد البارت مفرغ بالصوت والكتابة ، بتلاقوا إشارة السماعة فوق عاليسار من كل سلايد ،
بعد ما تفتحوا الملف من أبليكيشن xodo

Anticancer Drugs
Part 1

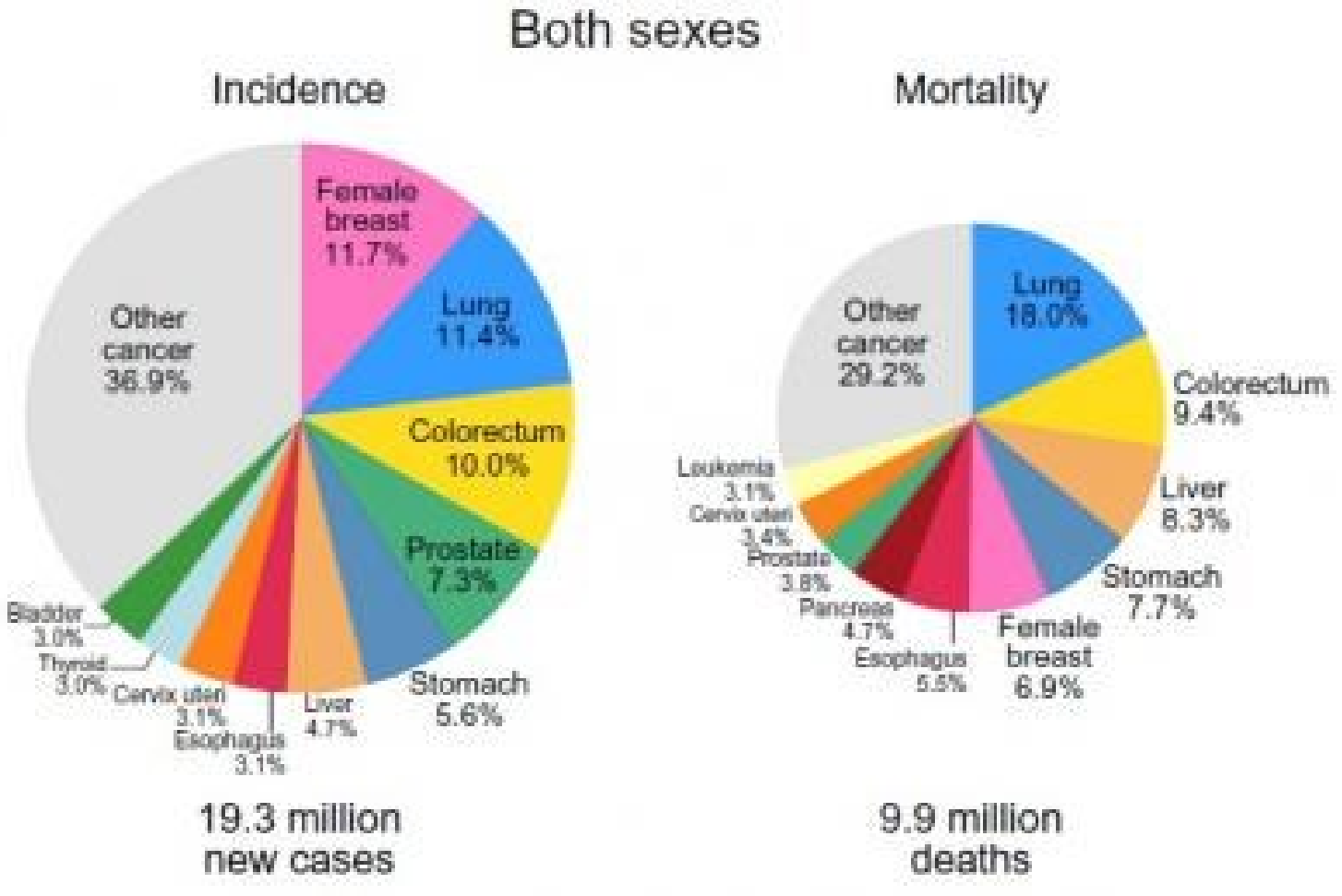
Heba Khader, Ph.D

Pharmacology 3

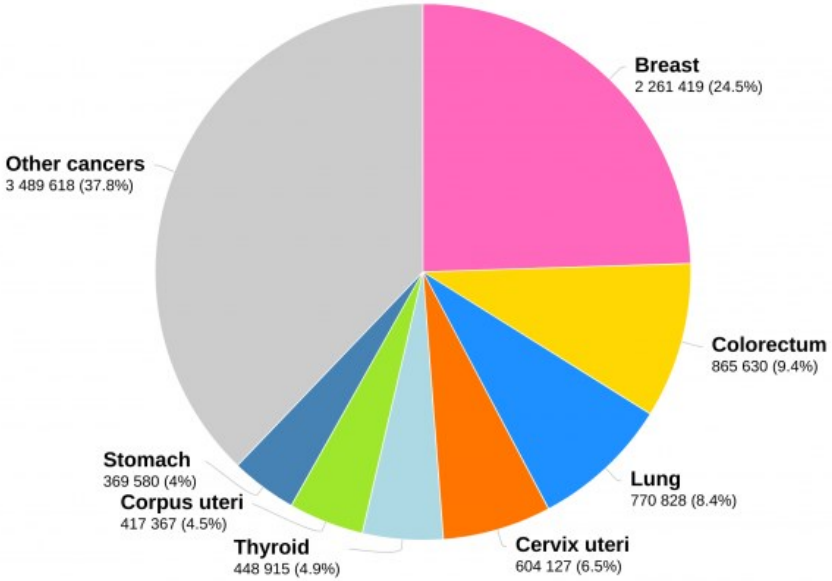
بهاد الشابتر رح نحكي عن الكانسر وكيف صار من **normal cells** صارلها **mutation** وتحولت لخلايا سرطانية ، الكانسر منتشر كتير وحسب إحصائيات ف كان أكتر شي بين الرجال هو **lung cancer** وبين النساء هو **breast cancer** طبعًا هالشي بكون حسب اختلاف بالجينات والتدخين والحياة الطبيعية وغيرها ، الكانسر كل ما اكتشفناه بمراحل مبكرة بكون علاجه أفضل ، حكيت هاي المقدمة لحتى أعمل سكيب عن أول ٤ سلايدات و إلّي هي مجرد إحصائيات بإصابات الكانسر

The problem

- Cancer is a leading cause of death worldwide, accounting for 9.9 million deaths in 2020.

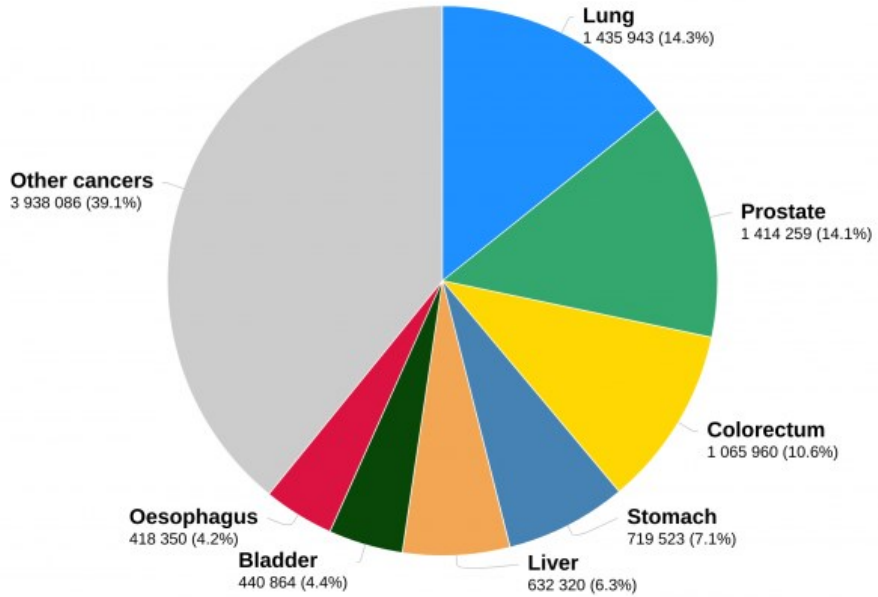


Estimated number of new cases in 2020, worldwide, females, all ages



Total : 9 227 484

Estimated number of new cases in 2020, worldwide, males, all ages



Total : 10 065 305

Ten most common cancer among Jordanian, Female

as in 2011

Primary Site	No. of Cases	%
Breast	935	37.7
Colorectal	233	9.4
Thyroid	145	5.8
Uterus	138	5.6
Non- Hodgkin Lymphoma	100	4.0
Leukemia	98	4.0
Ovary	70	2.8
Brain & Nervous System	67	2.7
Hodgkin Lymphoma	53	2.1
Cervix	51	2.1

Ten most common cancer among Jordanian, Male

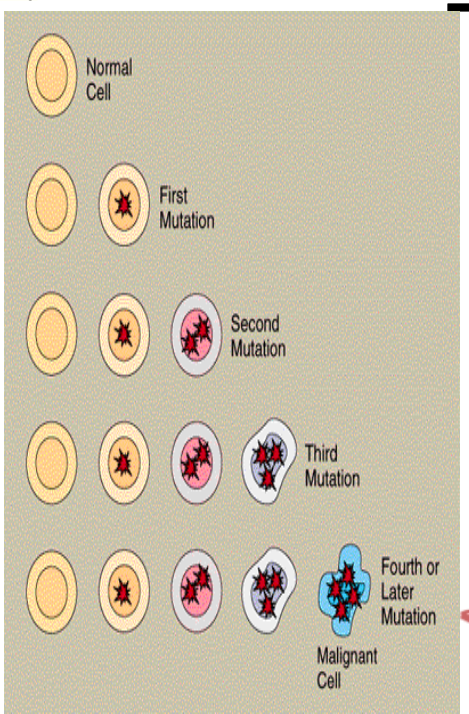
as in 2011

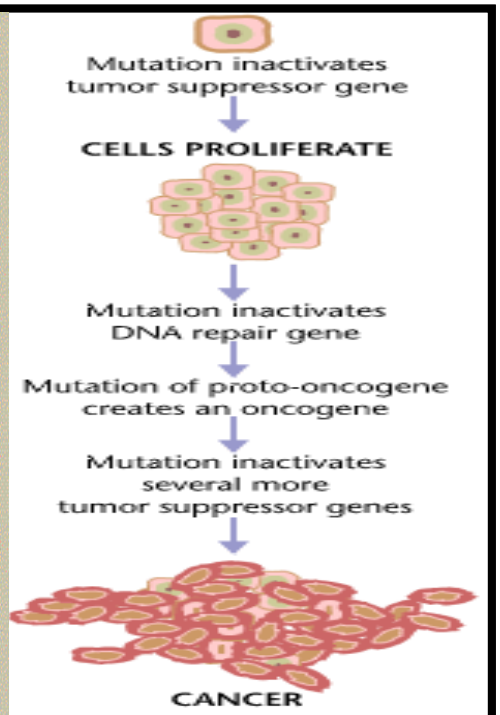
Primary Site	No. of Cases	%
Lungs	279	12.7
Colo-rectal	278	12.7
Bladder	171	7.8
Prostate	169	7.7
Leukemia	128	5.8
Non- Hodgkin Lymphoma	120	5.5
Brain &CNS	108	4.9
Stomach	81	3.7
Larynx	79	3.6
Hodgkin Lymphoma	71	3.2

الخلايا السرطانية بتنتج من خلية طبيعية تحولت ل **tumour cells** بعدة مراحل
من خصائص هاي الخلية السرطانية هي :

- Cancer arises from one single cell. The transformation from a normal cell into a tumour cell is **a multistage process**.
- Cancer cells are altered host cells:
  - shorter cell cycle (accelerated)
  - excessive proliferation
  - higher activity of nucleic acid and protein synthesis
  - altered cell-cell communication
  - invasive (disrupt normal healthy tissues)
  - migration to distant sites - metastasis

دورة حياتها قصيرة لإنها بتحدث بسرعة جدًا وتتكاثر بشكل مفرط ونشاطها أسرع من ناحية تكوين البروتينات وال **nucleic acid** وبتهاجم خلايا طبيعية وبتعمل خلل فيها
وإذا انتقلت من مكان إلى آخر هون حنسمّيها **metastasis** يعني ورم خبيث !
بالصورة بوضّحلنا **several mutation** صارت ب **several genes**





Treatment

- A correct cancer diagnosis is essential for adequate and effective treatment because every cancer type requires a specific treatment regimen.
- Treatment encompasses one or more modalities such as surgery, and/or radiotherapy, and/or chemotherapy.
- The primary goal is to cure cancer and improving the patient's quality of life.

التشخيص الصحيح بالكانسر هو الجزء الأكبر من العلاج والأهم لإنه
كل نوع من أنواع الكانسر بيحتاج لعلاج مناسب إله
في ٣ أنواع من علاجات الكانسر وكلهم هدفهم إني أحسّن نوعية حياة
المريض
surgery, radiotherapy, chemotherapy

PRINCIPLES OF CANCER CHEMOTHERAPY

إلها تأثير قاتل ومميت على الخلايا السرطانية

- Cause a lethal cytotoxic event or apoptosis in the cancer.
- Generally directed toward DNA or against metabolic sites essential to cell replication

  بتشتغل على ال **DNA + metabolic sites of cell replication**

  – for example, the availability of purines and pyrimidines.
- Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells.
- Unfortunately, most anticancer drugs do not specifically recognize neoplastic cells but, rather, affect both normal and abnormal cells.

ما بتشتغل فقط على الخلايا السرطانية وإنما على الخلايا الطبيعية والغير طبيعية

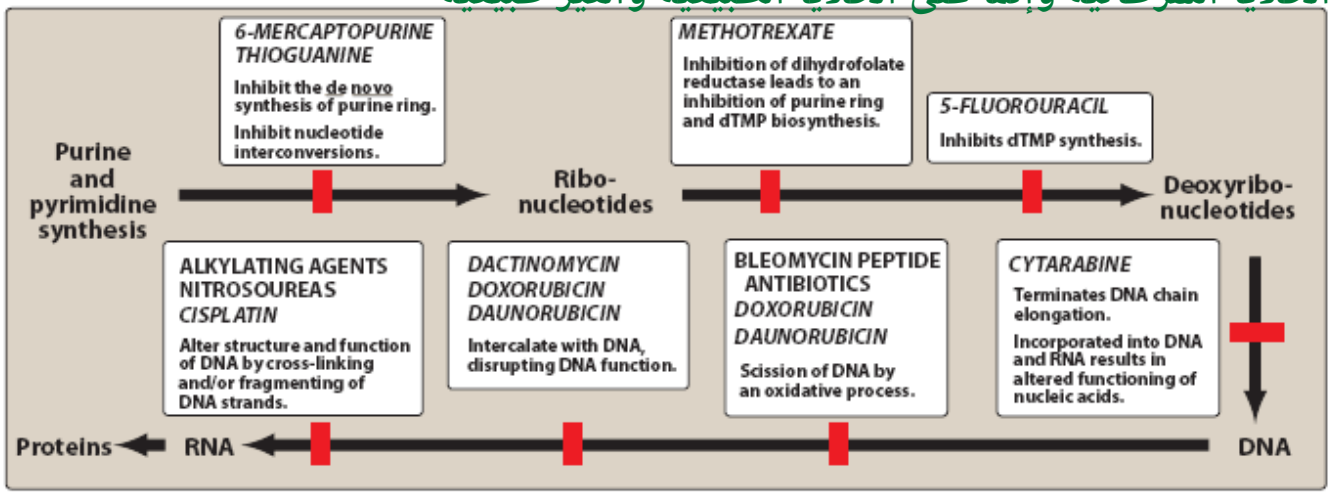


Figure 39.2
Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.

الصورة حنعمللها سكيب وبنرجع بأخر الشابتر وقت نتعرف كل دوا وين وشو ح يشتغل

Treatment strategies

- **1. Goals of treatment:**
  - The ultimate goal of chemotherapy is a cure (long-term, disease-free survival).
  - A true cure[1] requires the eradication of every neoplastic cell.
  - If a cure is not attainable, then the goal becomes control of the disease[2] (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life (palliative therapy).

بال **chemotherapy** أما بكون هدفي هو اني اعمل **true cure** يعني استئصل كل الخلايا السرطانية ف بضل المريض متعافي منه لأطول فترة ممكنة ، لكن إذا ما قدرت أعمل هيك
ف بصير هدفي اعمل **control** على المرض بحيث إني أوقف تقدمه وتطوره وتفاقمه وبهيك بكون حسّنت نوعية حياة المريض بما يسمى **palliative therapy**

متى بستخدم ال chemotherapy?

Treatment strategies

2. Chemotherapy is indicated when:

وقت تنتشر هاي الخلايا السرطانية ومش قادرين نعمل جراحة

- Neoplasms are disseminated and are not amenable to surgery.
- Also used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, (adjuvant chemotherapy).

بعد الجراحة أو radiotherapy بستخدمه لحتى اتخلص من اي جزئيات بسيطة ضايلة من الكانسر

- Prior to the surgical procedure in an attempt to shrink the cancer (neoadjuvant chemotherapy)

العكس ، يعني قبل العملية الجراحية لحتى أقلل من وجودها قدر المستطاع

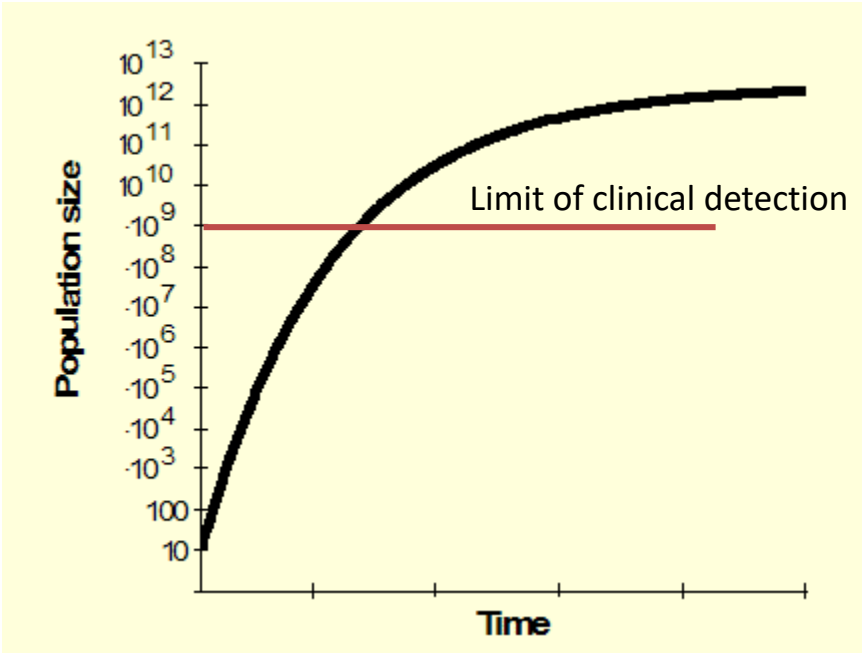
- Also given in low doses to assist in prolonging a remission (maintenance chemotherapy).

بفترة اختفاء أو تقليل أعراض المرض بنعطيه بجرعات منخفضة

Cell growth kinetics

كل ما كان الورم متضخم اكتر حتكون نسبة الخلايا إلّي انقسمت أو إلّي حضرت حالها للإنقسام(cell
growth fraction)أقل لإنه ما حيوصللها nutrients and blood supply for replication

- **Cell growth fraction** is the proportion of cells in the tumor dividing or preparing to divide. As the tumor enlarge, the cell growth fraction decreases because a large proportion of cells may not be able to obtain adequate nutrients and blood supply for replication.
- **Tumor doubling time** is the time for the tumor to double in size. As the tumor gets larger, its doubling time gets longer.



Gompertzian Growth Curve

هو الوقت إلّي حيتضاعف فيه حجم الورم للضغف ، ف كل ما كان الورم حجمه أكبر حيحتاج tumer
doupling time أطوَل لحتى يصير الضعف

بتبيّن تظهر أعراض الكانسر عالمريض بعد فترة متقدمة من المرض ف بالتالي بكون علاجه أصعب

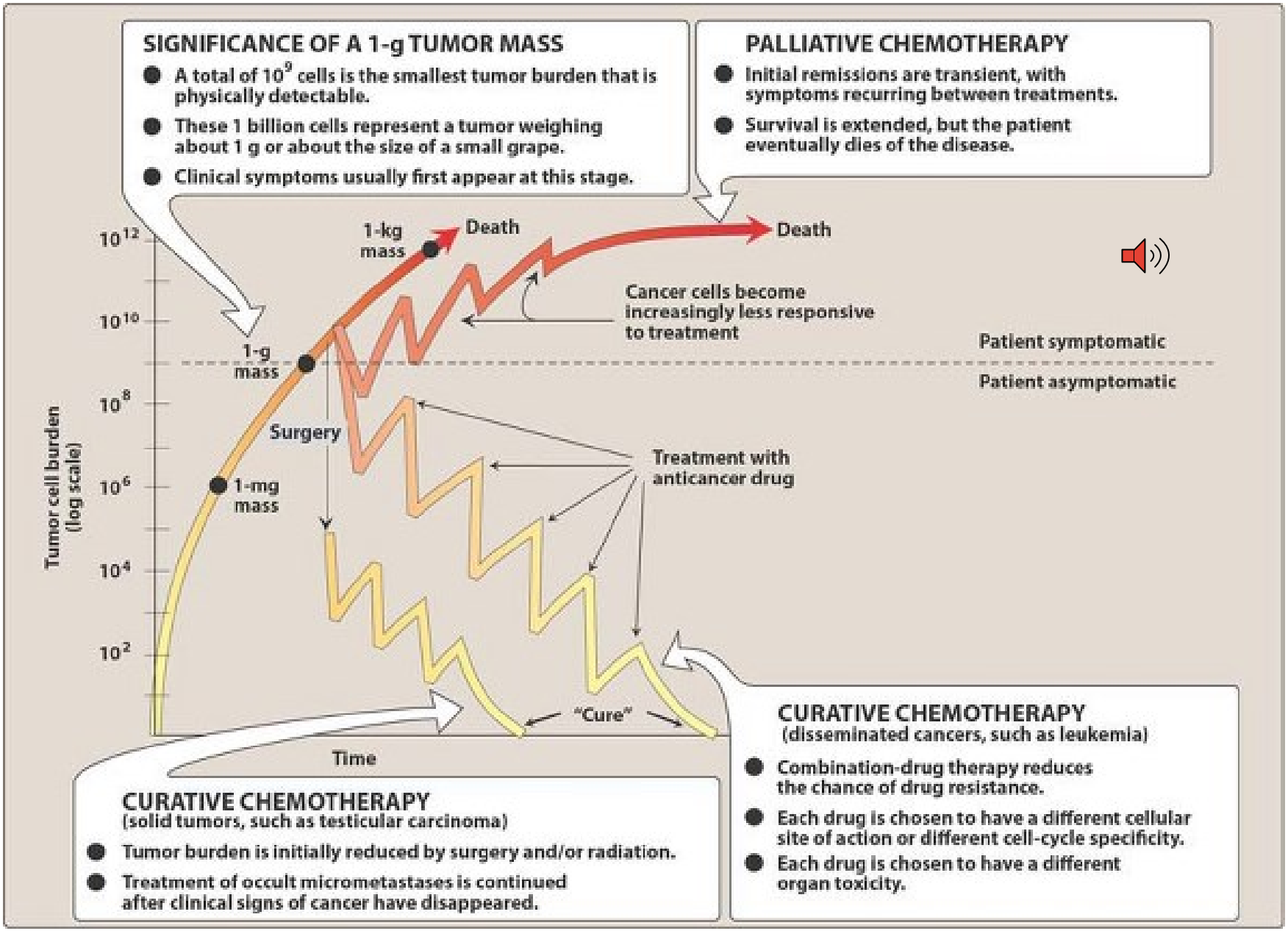
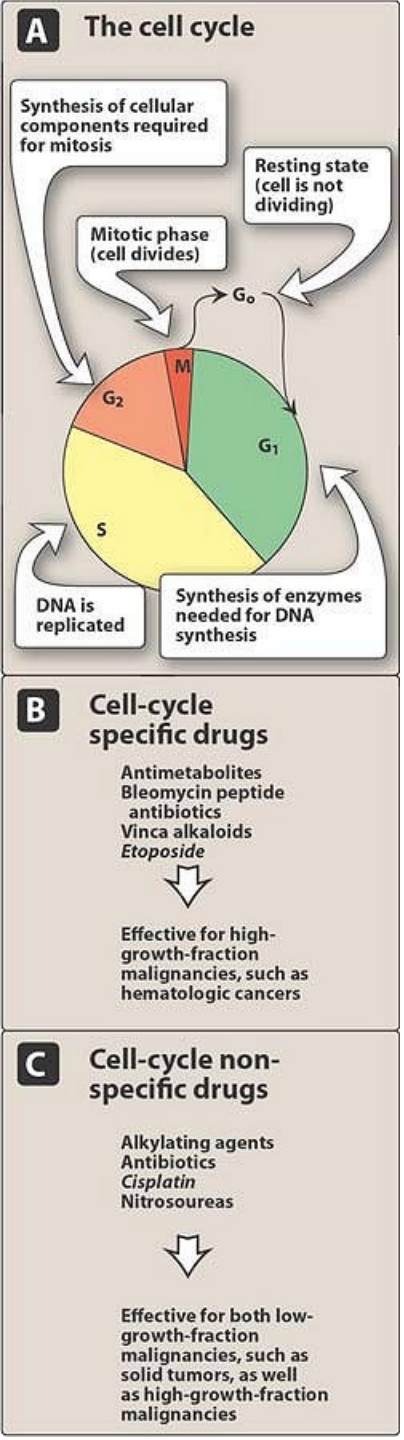


Figure 39.3 Effects of various treatments on the cancer cell burden in a hypothetical patient.

Treatment strategies



3. Tumor susceptibility and the growth cycle:

كل ما كان انقسام الخلايا أسرع = استجابتها للعلاج أفضل

- The fraction of tumor cells that are in the replicative cycle ("cell growth fraction") influences their susceptibility to anticancer agents.
- Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas slowly proliferating cells are less sensitive to chemotherapy. In general, nonproliferating cells (those in the G0 phase) usually survive the toxic effects of many of these agents.

- Chemotherapeutic agents may be classified according to their reliance on cell cycle kinetics for their cytotoxic effect:

a. **Cell-cycle specific drugs:** are effective only against replicating cells (that is, those cells that are cycling).

b. **Cell-cycle non-specific drugs:** used for replicating and non-replicating cells

تأثير العلاجات رح نحكي عنهم
بالتفصيل بالسلايدات الجاية ف
سكيب أعزائي

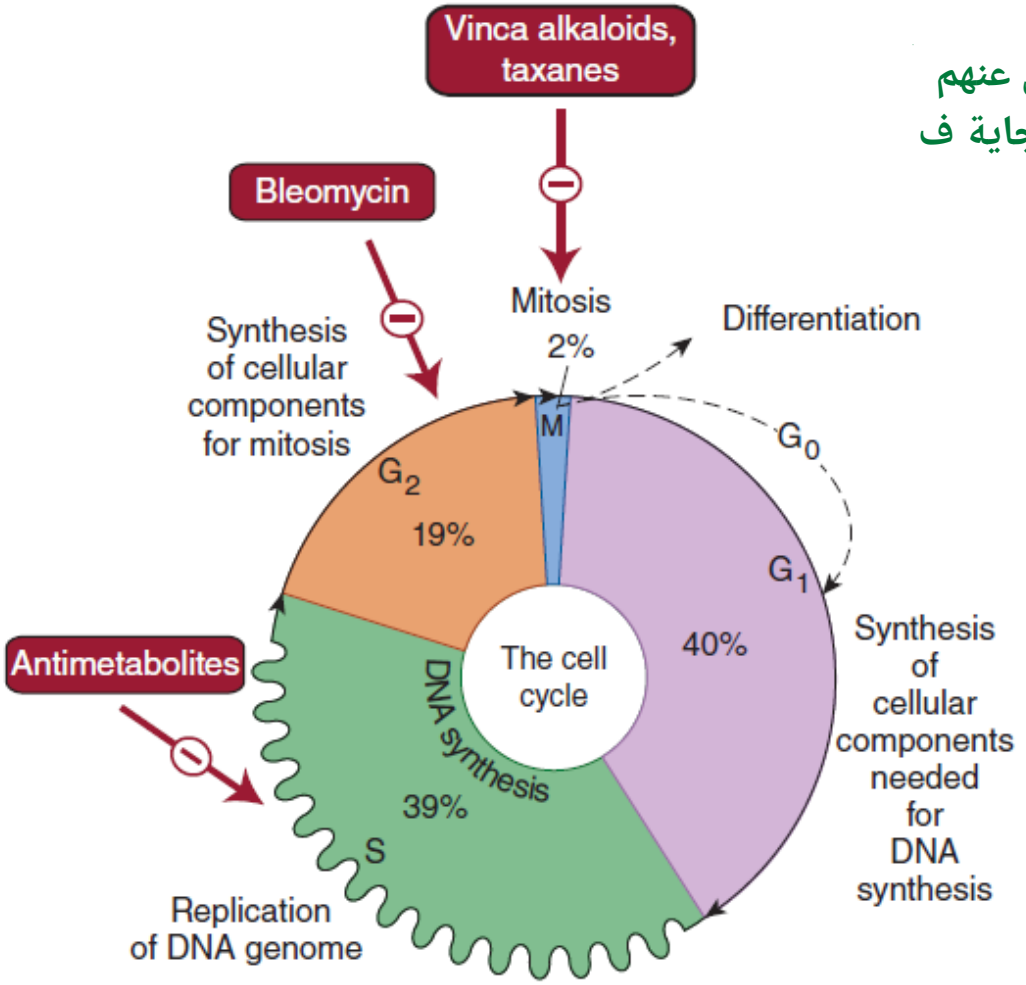


FIGURE 54–1 Phases of the cell cycle that are susceptible to the actions of cell cycle-specific (CCS) drugs. All dividing cells—normal and neoplastic—must traverse these cell cycle phases before and during cell division. Tumor cells are usually most responsive to specific drugs (or drug groups) in the phases indicated. Cell cycle-nonspecific (CCNS) drugs act on tumor cells while they are actively cycling and while they are in the resting phase (G_0). (Reproduced and modified, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 54–2.)

Treatment regimens and scheduling

- **The Log-Kill Hypothesis**
- In cancer chemotherapy, destruction of cancer cells follows first-order kinetics (a given dose of drug for a defined time period destroys a constant fraction of cells regardless the absolute number of cells, this is called LOG KILL or fraction kill).
- A key principle that stems from this finding and that is applicable to hematologic malignancies is an inverse relationship between tumor cell number and curability.

العلاج بال **chemoreceptors** بيتبع ال **first order kinetic** بمعنى إنه
وقت أعطي جرعة معينة من العلاج لفترة معينة من الوقت رح تعمل **destroy** ل
constant fraction يعني نسبة محددة من الخلايا السرطانية بغض النظر عن العدد

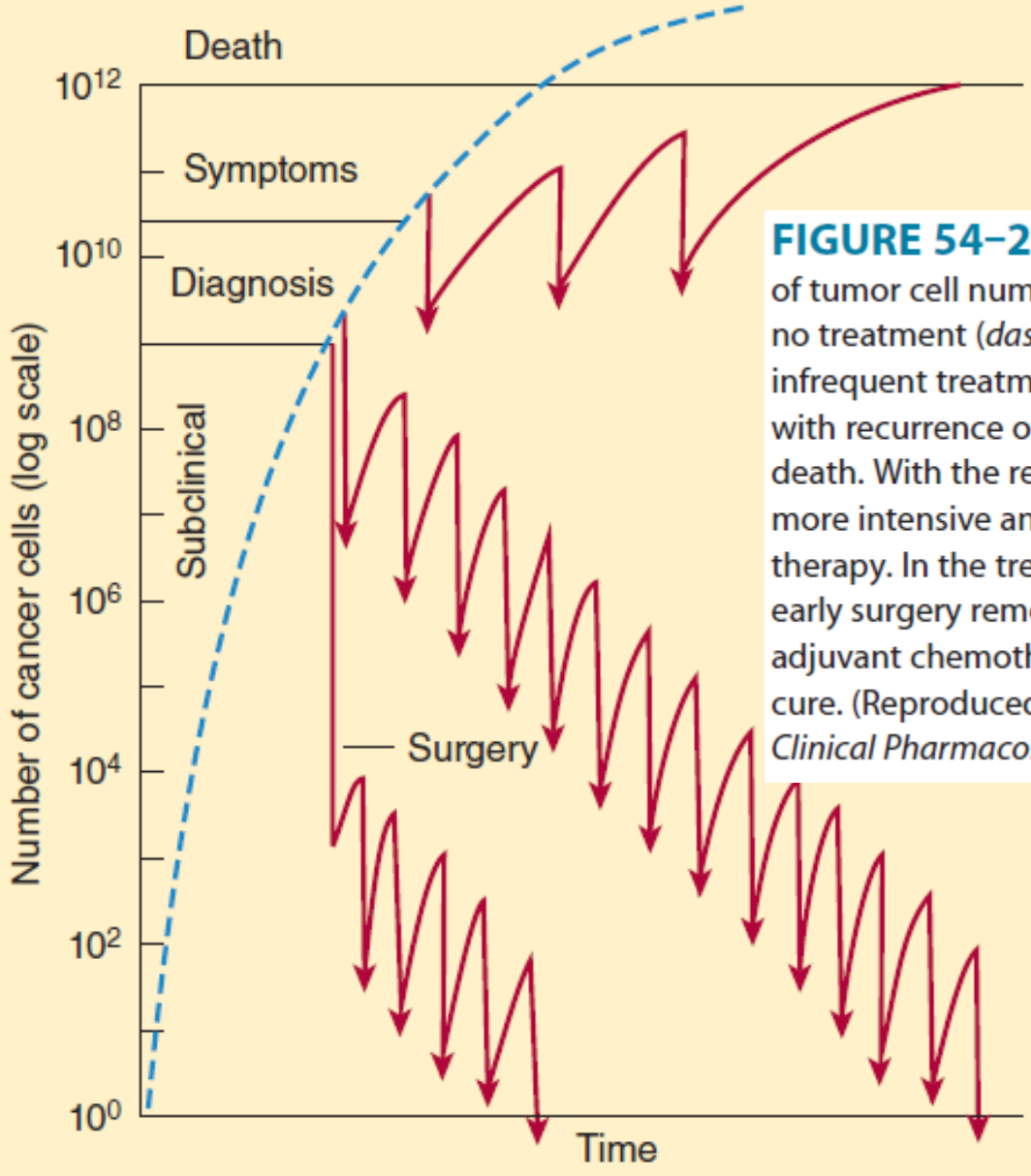


FIGURE 54–2 Relationship, based on the log-kill hypothesis, of tumor cell number to 3 approaches to drug treatment and to no treatment (*dashed line*). In the protocol diagrammed at the top, infrequent treatment (indicated by *arrows*) prolongs survival but with recurrence of symptoms between treatments and eventual death. With the regimen diagrammed in the middle section that is more intensive and begun earlier, cure results after many cycles of therapy. In the treatment diagrammed near the bottom of the graph, early surgery removes much of the tumor burden, and intensive adjuvant chemotherapy has been used long enough to produce a cure. (Reproduced with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 54–1.)

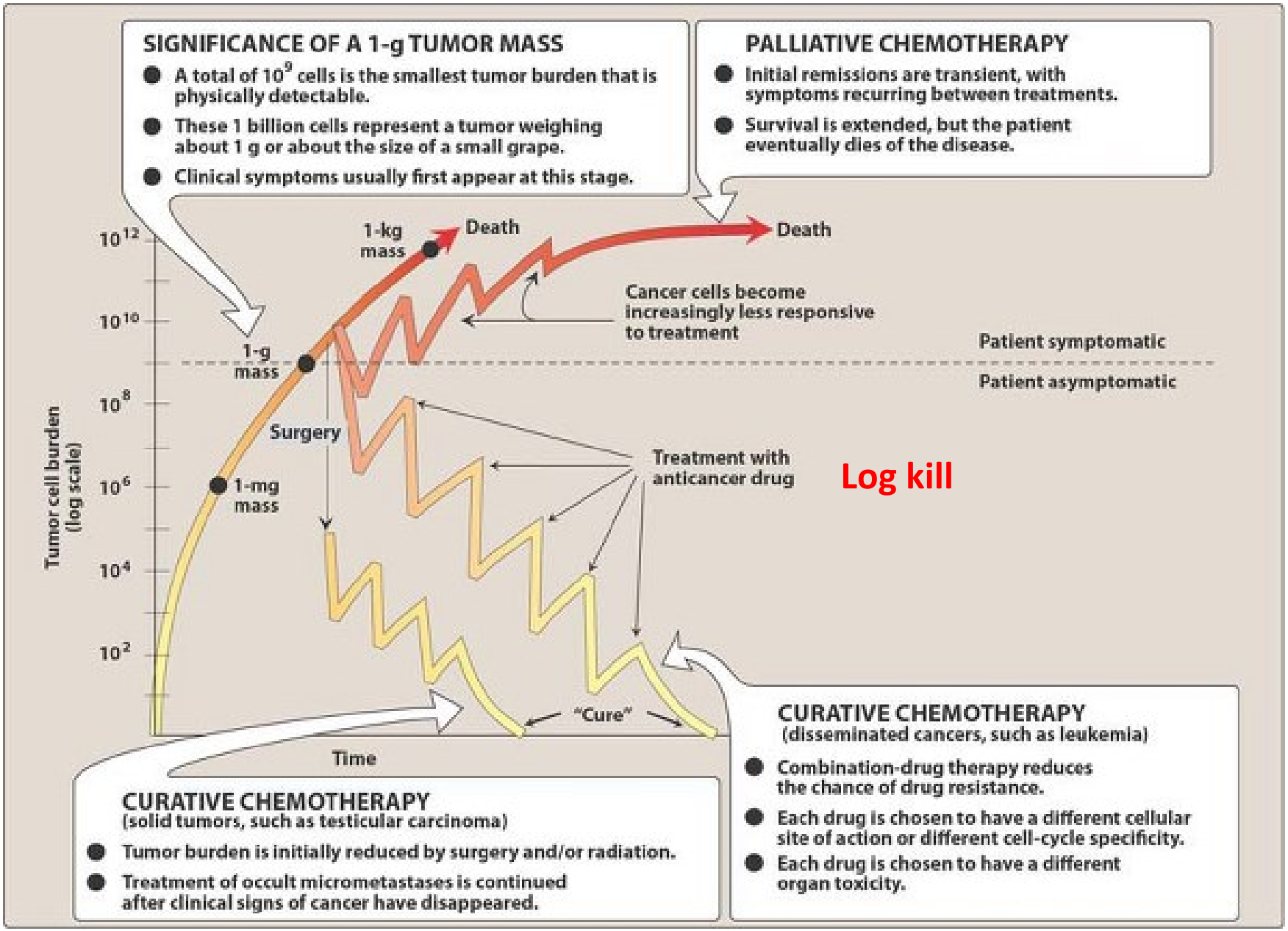


Figure 39.3 Effects of various treatments on the cancer cell burden in a hypothetical patient.

Treatment regimens and scheduling

- Chemotherapy dosing may be based on **body weight**, body surface area **(BSA)** or area under the concentration versus time curve **(AUC),** with an effort being made to tailor the medications to each patient.
- BSA is most frequently used because it provides an accurate comparison of activity and toxicity across species. In addition, BSA correlates with cardiac output, which determine renal and hepatic blood flow and thus affects drug elimination.
- **Dosing adjustments** may be required for kidney and liver dysfunction to prevent toxicity.

بعطي جرعة ال **chemotherapy** حسب **body weight+**
BSA + AUC لكن أكتر طريقة معتمدة هي ال **BSA** لعدة أسباب عليهم هايلايتر

وبحتاج إني أعمل **dose adjustment** في حالة ال **kidney and liver dysfunction**

Treatment protocols

- **Drug combination** is more successful than single drug treatment in most cancers.

استخدام ال **combination** بعلاج الكانسر أحسن من استخدامه لوحده

- The following principles are important for selecting appropriate drugs to use in combination chemotherapy:

شروط استخدام ال **combination** :

(1) Each drug should be active when used alone against the particular cancer.

لو بدي استخدم الدوا لحاله لازم يكون إله تأثير على الخلايا السرطانية

(2) The drugs should have different mechanisms of action.

بختلفوا بالميكانيزم

(3) Cross-resistance between drugs should be minimal.

ما يكون في **cross toxicity**

(4) The drugs should have different toxic effects

وتأثيرهم عالخلايا مختلف

- The advantages of combinations:

فوائد إني استعمل ال **combination**:

  - Provide maximal cell killing within the range of tolerated toxicity
  - Effective against a broader range of cell lines in the heterogeneous tumor population
  - May delay or prevent the development of resistant cell lines.

- Many cancer treatment protocols have been developed, and each one is applicable to a particular neoplastic state

تم تطوير العديد من العلاجات السرطانية وبنستخدمهم حسب نوع الكانسر

مثال على ال **regimen** في علاج اللوكيميا

Drug Regimen

Course 1: Hyper-CVAD (Cycles 1, 3, 5, & 7)

Days	Drug	Dose	Route	Comments
1-3	Cyclophosphamide	300mg/m²	IV over 2hrs, 12hrly total of 6 doses.	Mesna see below
4-5	Doxorubicin	50mg/m²	IV continuously over 48hrs	
4 & 11	Vincristine	1.4mg/m²	Intravenous infusion in 50ml sodium chloride 0.9% over 10 minutes, as per national guidance. Nurse to remain with patient throughout infusion	Maximum 2mg
1-4 11-14	Dexamethasone	40mg	Oral, daily	

Course 2: MTX/ARA-C (Cycles 2, 4, 6, & 8)

Days	Drug	Dose	Route	Comments
1-2	Methotrexate	1g/m²	IV for 24hrs continuously	200mg/m² for 2hrs then 800mg/m² for 22hrs
2-3	Cytarabine	3g/m²	IV over 2hrs, 12hrly total of 4 doses	

Cycle Frequency

Every 21 days up to 8 cycles

سكيب 😀

TABLE 54–1 Selected examples of cancer chemotherapy. (*Do not attempt to memorize type of treatment for each cancer. In this chapter focus on the drugs' mechanism of action, dose-limiting adverse effects and general mechanisms of resistance*).

Diagnosis	Examples of Commonly-Used Anticancer Drugs
Acute lymphocytic leukemia in children	Prednisone, vincristine, and asparaginase or an anthracycline, plus intrathecal methotrexate
Acute myelogenous leukemia in adults	Cytarabine and idarubicin or daunorubicin
Breast carcinoma	Cytotoxic agents, hormonal therapy with tamoxifen or an aromatase inhibitor (eg, anastrozole), trastuzumab
Chronic myelogenous leukemia	Imatinib, newer tyrosine kinase inhibitors, interferon
Colon carcinoma	Fluorouracil plus leucovorin plus oxaliplatin
Hodgkin's lymphoma	ABVD regimen: doxorubicin (Adriamycin), bleomycin, vincristine, dacarbazine, and prednisone
Non-Hodgkin's lymphoma	CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab
Ovarian carcinoma	Paclitaxel and carboplatin
Pancreatic carcinoma	Gemcitabine and erlotinib
Prostate carcinoma	GnRH agonist (eg, leuprolide) or antagonist (eg, abarelix) and androgen receptor antagonist
Lung carcinoma	Carboplatin, paclitaxel, and bevacizumab
Testicular carcinoma	PEB regimen: cisplatin (Platinol), etoposide, and bleomycin

GnRH, gonadotropin-releasing hormone.

Acronyms often are used to designate chemotherapy regimen

Problems associated with chemotherapy

A. Resistance:

كيف الخلايا السرطانية بتعمل **resistance** على أدوية الكانسر ؟

- Drug resistance is a major problem in cancer chemotherapy.
- Mechanisms of resistance include the following:

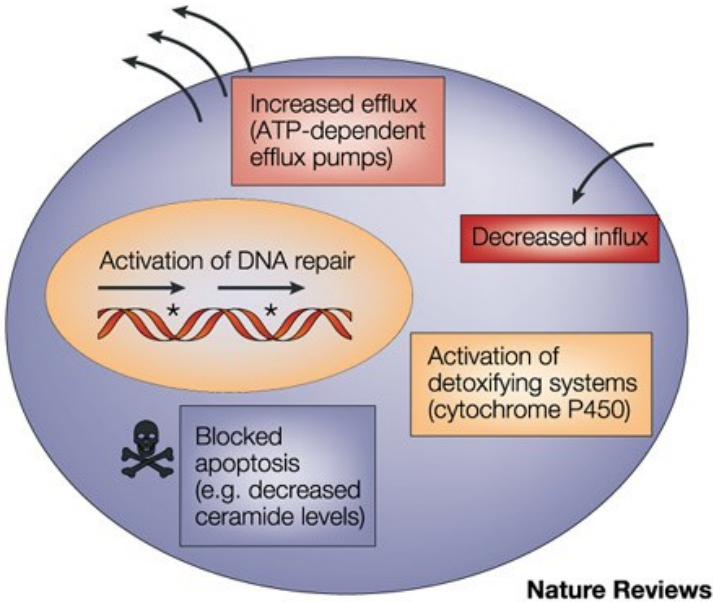
1. Increased DNA repair—An increased rate of DNA repair in tumor cells can be responsible for resistance and is particularly important for alkylating agents and cisplatin.

بتزيد ال **rate of DNA repair** المسؤول عن ال **resistance**

2. Formation of trapping agents—Some tumor cells increase their production of thiol trapping agents (eg, glutathione), which interact with anticancer drugs that form reactive electrophilic species. This mechanism of resistance is seen with the alkylating agent bleomycin, cisplatin, and the anthracyclines.

تكوين ال **tapping agent** حتعمل مع **reactive electrophilic**
أدوية الكانسر ف بوقف مفعولها

3. Changes in target enzymes—Changes in the drug sensitivity of a target enzyme, dihydrofolate reductase, and increased synthesis of the enzyme are mechanisms of resistance of tumor cells to methotrexate.



Problems associated with chemotherapy

4. Decreased activation of prodrugs— Resistance to the purine antimetabolites (mercaptopurine, thioguanine) and the pyrimidine antimetabolites (cytarabine, fluorouracil) can result from a decrease in the activity of the tumor cell enzymes needed to convert these prodrugs to their cytotoxic metabolites.

5. Inactivation of anticancer drugs— ncreased activity of enzymes capable of inactivating anticancer drugs is a mechanism of tumor cell resistance to most of the purine and pyrimidine antimetabolites.

6. Decreased drug accumulation

This form of multidrug resistance involves the increased expression of a normal gene (MDR1) for a cell surface glycoprotein (P-glycoprotein).

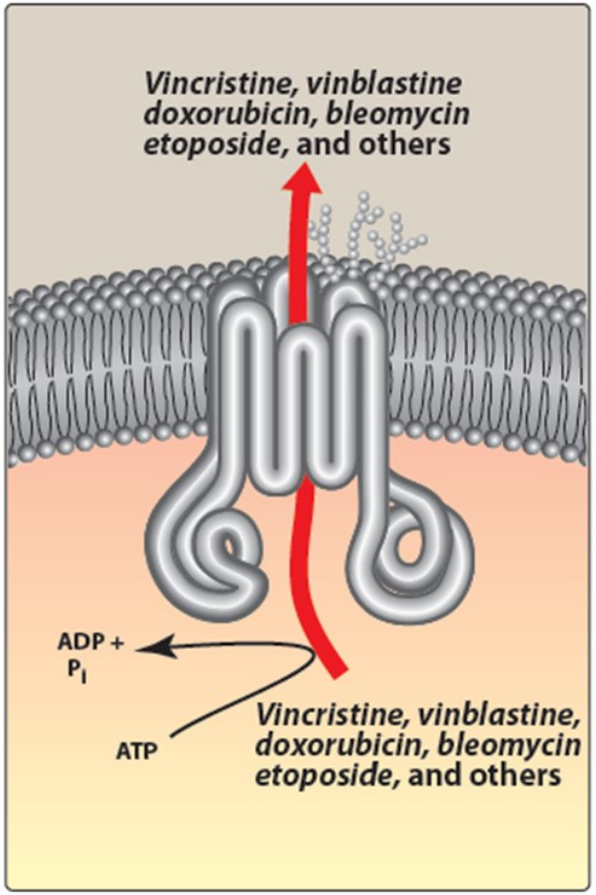


Figure 39.5
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

٤) بقلل ال **activity** للإنزيمات المسؤولة عن تحويل ال **anti cancer pro drug** ل **cytotoxic metabolites** وهاد بنشوفه بأدوية ال **pyrimidine and purine antimetabolites**

٥) بنعمل **inactivation** للدوا عن طريق إنزيمات موجودة بال **tumer cells** وبرضو هالشي بنشوفه بأدوية ال **pyrimidine and purine antimetabolites**

٦) بنمنع تراكم الدوا ورح نحكي عنها أكتر بعدين بس بكون عن طريق زيادة ال **expression of a normal gene** الموجود على **cell surface glycoprotein**

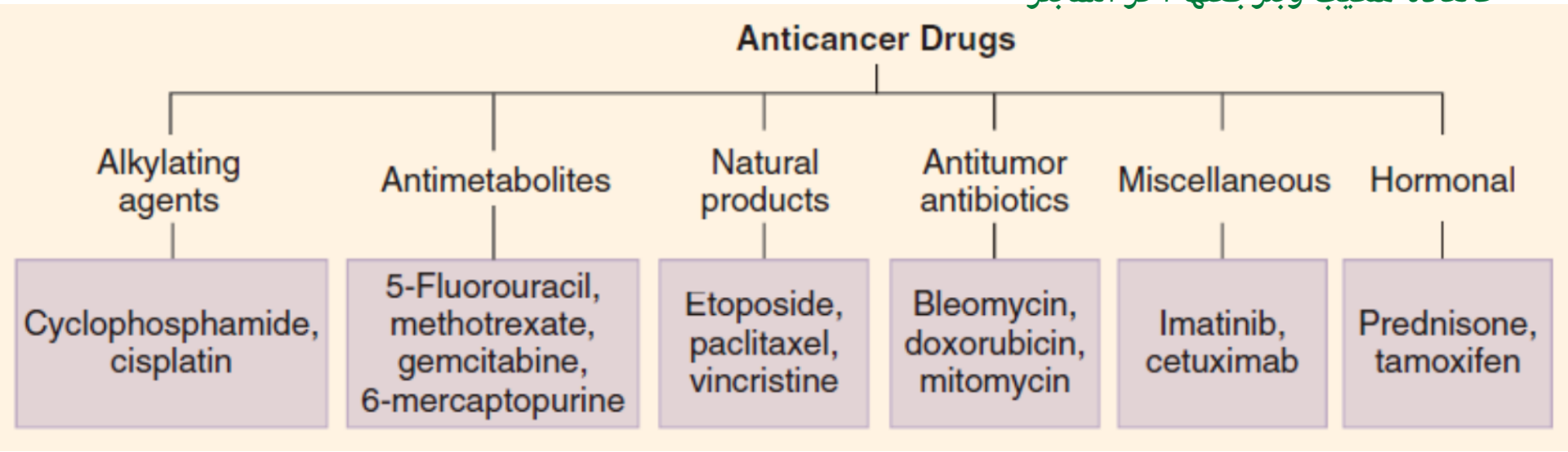
Problems associated with chemotherapy

B. Toxicity:

- Therapy also affects normal cells undergoing rapid proliferation (buccal mucosa, bone marrow, gastrointestinal (GI) mucosa, and hair), contributing to the toxic manifestations of chemotherapy.
- Severe vomiting (use antiemetic), stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents.
- The duration of side effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities are irreversible.
- Some toxic reactions may be ameliorated by interventions:
  - Cytoprotectant drugs as prostaglandins to protect the GIT from ulcer
  - Perfusing the tumor locally
  - Removing some of the patient's marrow prior to intensive treatment and then reimplanting it.
  - Promoting intensive diuresis to prevent bladder toxicities.
  - The megaloblastic anemia that occurs with methotrexate can be effectively counteracted by administering folinic acid (leucovorin, 5-formyltetrahydrofolic acid)

أي خلية بتكون rapid proliferation حتى لو كانت طبيعية نورمال رح تتأثير بال chemotherapy
ومن الأعراض إلّي حنواجهها بهاي الحالة ححط عليها هايلايتر بس ال alopecia معناها ثعلبة
وبتختلف هاي الأعراض من ناحية مدتها أو حدتها حسب نوع العلاج المستخدم
كيف ممكن أحل المشاكل الناتجة من ال toxic reaction هاد ؟:
١) بعطيه prostaglandins as cytoprotectant drug لحتى أحميه من ال GI ulceration
٢) ازلنا جزء من ال bone marrow نخاع العظم خلال فترة العلاج المكثف وبعدها بنرجع نزرعه تاني لحتى ما يصير عنده bone marrow suppression
٣) بنعطي للمريض مدرات بول diuresis لحتى ما تحتبس السوائل عنده ويصير معه bladder toxicity
وأخر شي العرَض الناتج من استخدام ال methotrexate تحديدًا هو ال megaloblastic anemia وعلاجه أعطيه folinic acid supplement

كالعادة سكيب وبنرجعلها اخر الشابتر



Antimetabolites

بشبهوا بالستركشر الفوليك اسيد وتركيبات تانية مهمة بال **metabolic**
processes زي ال **purine and pyrimidine** من خلال طريقتين ححط
عليهم هايلايتر

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

- Maximal cytotoxic effects are in S-phase (cell-cycle specific).

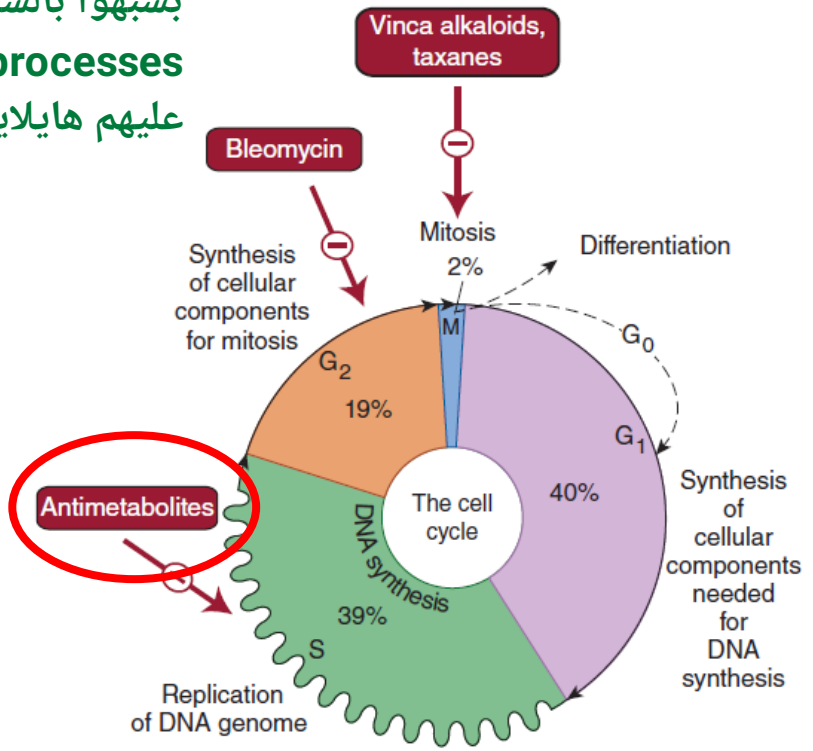


FIGURE 54–1 Phases of the cell cycle that are susceptible to the actions of cell cycle-specific (CCS) drugs. All dividing cells—normal and neoplastic—must traverse these cell cycle phases before and during cell division. Tumor cells are usually most responsive to specific drugs (or drug groups) in the phases indicated. Cell cycle-nonspecific (CCNS) drugs act on tumor cells while they are actively cycling and while they are in the resting phase (G_0). (Reproduced and modified, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 54–2.)

۳ چروبات بال anti metabolites حطیت هایلایترع اهم دوا بکل چروب

Antimetabolites

(Cell cycle specific)

Folate Antagonist

- Methotrexate
- Pemetrexed
- Pralatrexate

Purine Antagonists

(adenine and guanine)

- 6-thioguanine
- 6-mercaptopurine
- Fludarabine

Pyrimidine Antagonists

(thymidine, cytosine, and uracil)

- 5-fluorouracil
- Capecitabine
- Cytarabine (cytosine arabinoside)
- Gemcitabine

Methotrexate

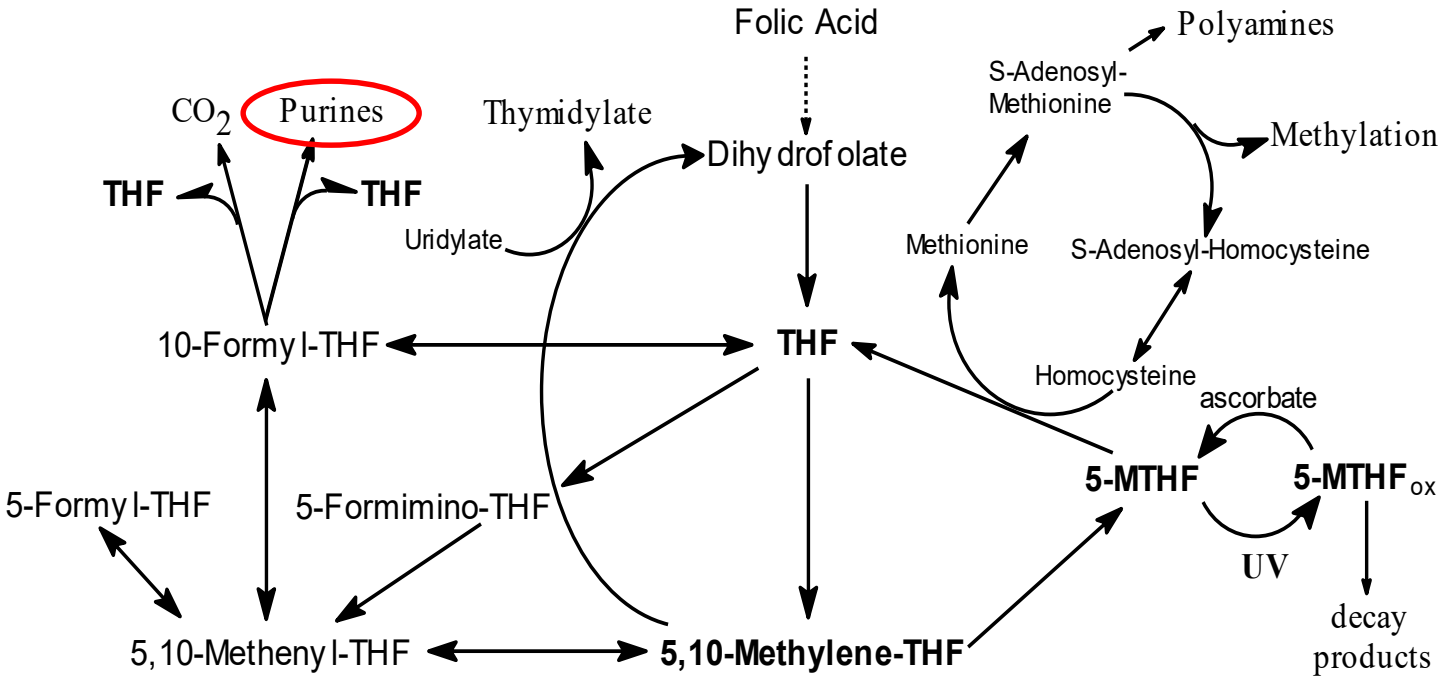
Mechanism of action:

- Methotrexate (MTX) is a folic acid analog that binds with high affinity to the active 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
  - amino acids serine and methionine
- Inhibition of these metabolic processes thereby interferes with the formation of DNA, RNA, and key cellular proteins.

بتشابه بالستركشر مع الفوليك اسيد ف بيرتبط بموقع ال
dihydrofolate reductase وبيعمللها **inhibition** وما حيتصنع
ال **tetrahydrofolate** و إلّي هو يُعتبر الناقل الوحيد للكربون
المسؤول عن تكوين الأشياء إلّي عليها هايلايتر
ف بالتالي ما حيتصنع عندي ال **precursors** إلّي بحتاجهم
بتصنيع ال **DNA, RNA, cellular protein**

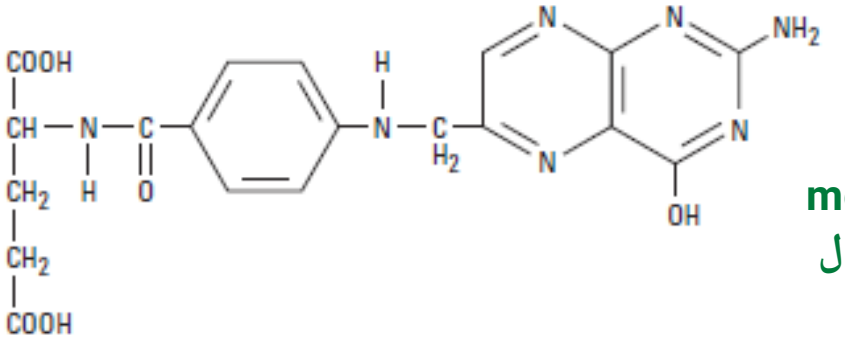
طبعًا الخلية بشكل طبيعي بتحتاج للفوليك اسيد لحتى تعمل
multiplication وعمليات تانية للخلية ، ف الخلية هون بتكون
ارتبطت بالغلط بال **methotrexate**

Organization of folate forms and their role in one-carbon metabolism

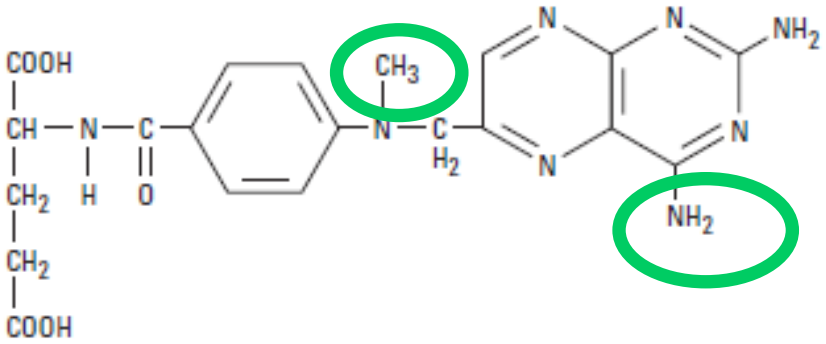


• Folate are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication.

MTX is a folic acid analog



Folic acid



Methotrexate

الفرق بالستركشر فقط بال **methyl**
الموجودين بال **and NH2 group**
methotrexate

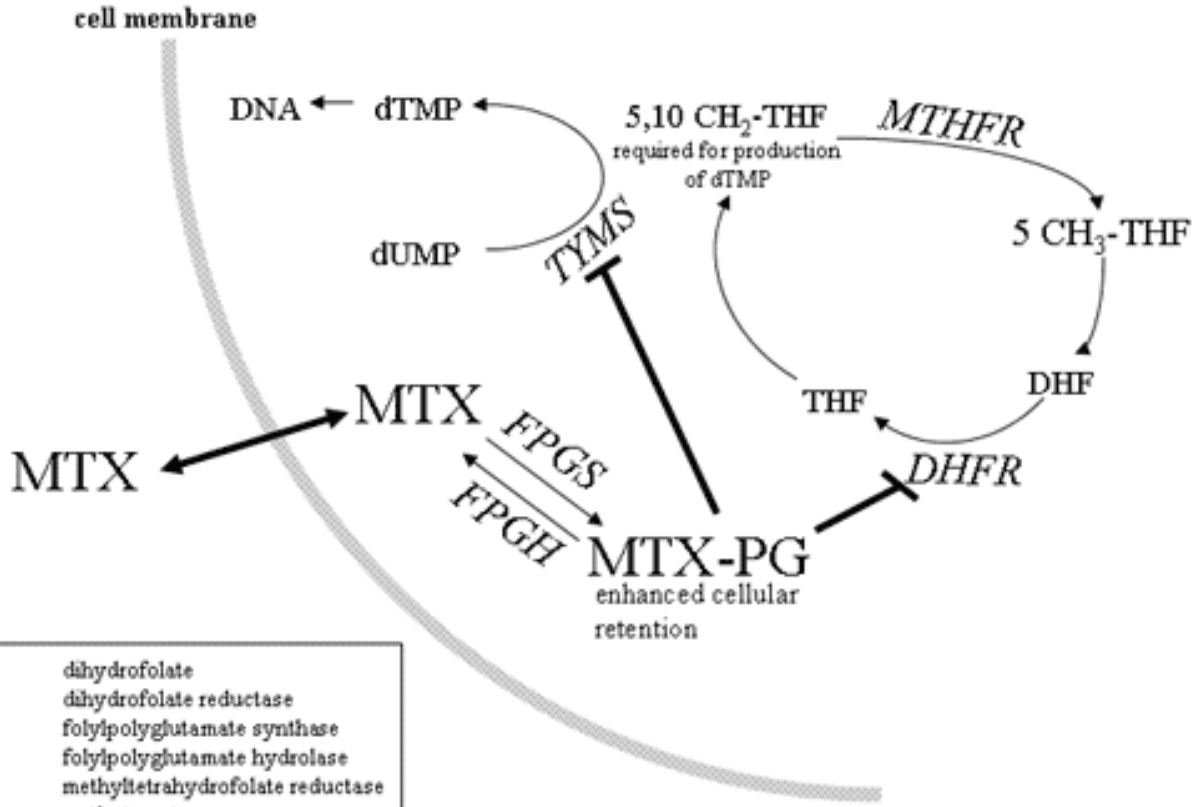
Methotrexate

- MTX is transported into the cell via the **reduced folate carrier**.
- Intracellular formation of **polyglutamate metabolites**, with the addition of up to 5–7 glutamate residues, is critically important for the therapeutic action of MTX, and this process is catalyzed by the enzyme **folylpolyglutamate synthase (FPGS).**
- MTX polyglutamates inhibit enzymes involved in de novo purine nucleotide and thymidylate biosynthesis, making them important determinants of MTX's cytotoxic action.

بدخل ال **methotrexate** لداخل الخلية عن طريق **reduced folate Carrier** وبعدها ح ييجي
انزيم هو بالأصل بيربط **polyglutamate metabolites 7-5** بالفوليك اسيد ، بس هون ح
يربطهم بال **Methotrexate**
وبعدها رح يشتغل ويعمل **inhibition**

Methotrexate cellular pharmacology

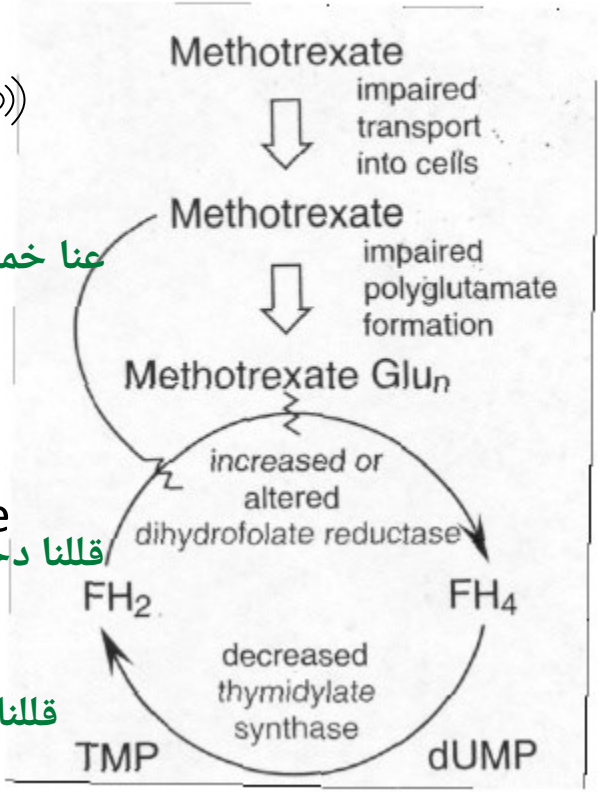
targets for pharmacogenetic analysis shown in italics



DHF	dihydrofolate
DHFR	dihydrofolate reductase
FPGS	folylpolyglutamate synthase
FPGH	folylpolyglutamate hydrolase
MTHFR	methyltetrahydrofolate reductase
MTX	methotrexate
MTX-PG	methotrexate polyglutamate
THF	tetrahydrofolate
5 CH_3-THF	methyl-THF
5,10 CH_2-THF	methylene-THF
TYMS	thymidylate synthase

Methotrexate Resistance

عنا خمس طرق حتعمل فيها الخلية السرطانية **resistance** تجاه ال **methotrexate**



- Several resistance mechanisms to MTX have been identified, and they include:
  - (1) decreased drug transport via the reduced folate carrier or folate receptor protein

    قللنا دخوله من خلال ال **carrier**
  - (2) decreased formation of cytotoxic MTX polyglutamates,

    قللنا من عملية تحويله ل **polyglutamate**
  - (3) increased levels of the target enzyme DHFR through gene amplification and other genetic mechanisms

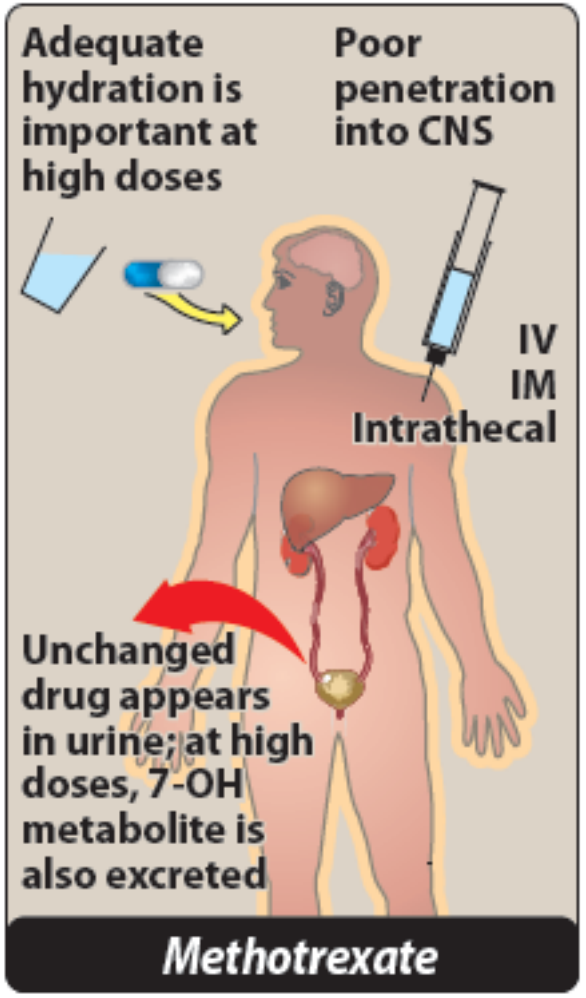
    بنزيد ال **dihydrofolate reductase** ف مش حيقدر يرتبط فيهم كلهم
  - (4) altered DHFR protein with reduced affinity for MTX.

    بنقلل ال **affinity** لارتباط ال **methotrexate** عالإنزيم اصلا
  - (5) decreased accumulation of drug through activation of the multidrug resistance transporter P170 glycoprotein.

    بنقلل تراكم الدوا بالجسم عن طريق ال **p170 glycoprotein**

Pharmacokinetics of MTX

- MTX is administered by the intravenous, intrathecal, or oral route. However, oral bioavailability is saturable and erratic at doses greater than 25 mg/m^2.
- **Renal excretion** is the main route of elimination and is mediated by glomerular filtration and tubular secretion. As a result, dose modification is required in the setting of renal dysfunction.
  - Care must also be taken when MTX is used in the presence of drugs such as aspirin, nonsteroidal anti-inflammatory agents, penicillin, and cephalosporins, as these agents inhibit the renal excretion of MTX.
- High doses of MTX undergo hydroxylation at the 7-position. This derivative is much less active, less water soluble and may lead to **crystalluria**. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity.



ال methotrexate ممكن ينعطى IV أو orally أو intrathecal مع هيك إذا كانت الجرعة أكتر من 25mg/m² ف رح تكون ال bioavailability إله قليلة كيف بصيرله excretion ؟ عن طريق ال glomerular filtration and tubular secretion
ف لهيك إذا كان في مشكلة بالرينال ف بنحتاج نعدل ال dose

من الأدوية إلّي بنقدر نعتبرها contraindications مع ال methotrexate هي ال aspirin and NSAIDs and penicillin and cephalosporin ليش ؟
لإنهم بيمنعوا ال MTX يطلع من الرينال

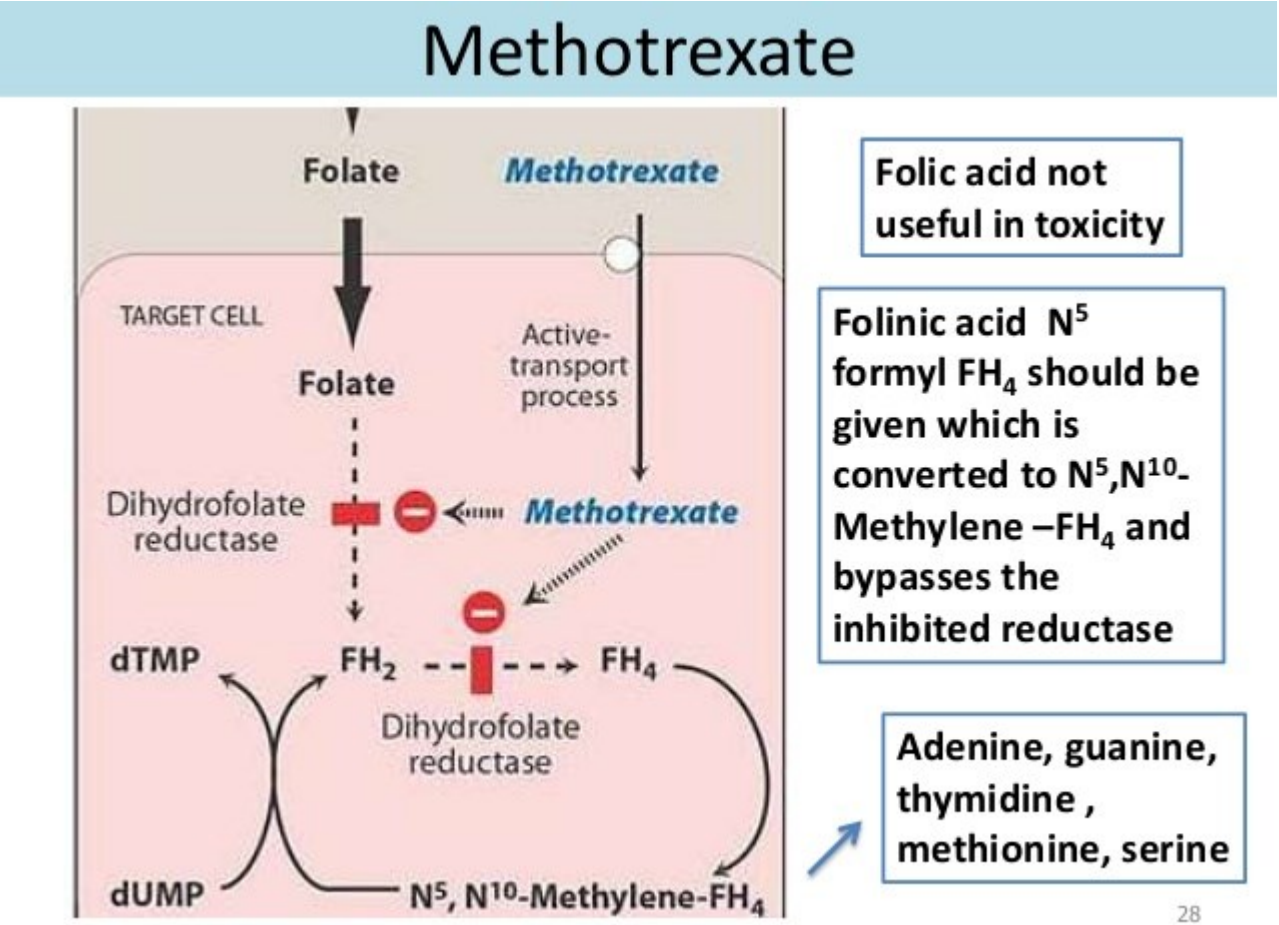
وقت ناخد جرعات عالية من ال MTX حيعمل hydroxylation على position 7 ف بالتالي حيصير less active, less water soluble ف بيعمل ال crystalluria إلّي حكينا عنها كتير وحكينا بنحل هاي المشكلة عن طريق إنه نخلي ال urine قاعدي لإنه ال MTX حمضي أو عن طريق إنه يشرب مي كتير ، ولو ما انحلت المشكلة للأسف ح يصير renal toxicity

Adverse effects of MTX

- Nausea, vomiting, and diarrhea, stomatitis, myelosuppression with neutropenia and thrombocytopenia. بيعمل نفس أعراض ال **folic acid deficiency**
- The biologic effects of MTX can be reversed by administration of the reduced folate **leucovorin** (5-formyltetrahydrofolate) or by L-leucovorin (which is the active enantiomer). Leucovorin is taken up more readily by normal cells than by tumor cells. بنعطي الفوليك اسيد هون ع شكل **leucovorin** يعني **Tetrahydrofolic acid** جاهز وبتستخدمهم الخلايا الطبيعية بشكل مباشر أكتر من الخلايا السرطانية
- Leucovorin rescue is used in conjunction with high-dose MTX therapy to rescue normal cells from excessive toxicity, and it has also been used in cases of accidental drug overdose. However, doses of leucovorin must be kept minimal to avoid possible interference with the antitumor action of MTX. بستخدمه بحالة الجرعات العالية من ال **MTX** أو تناول الكحول بالخطأ بس بنستخدمه بجرعات معينة
- Contraindications: It should be avoided in pregnancy.

Adverse effects of MTX

رسمة توضيحية لكلامنا السابق



Methotrexate (MTX)

Therapeutic uses:

بعلاج الكانسر بستخدمه مع أدوية تانية **as combination**

- MTX is used usually in combination with other drugs

من الأمثلة على أنواع الكانسر إلي بعالجها

- Effective against breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma.
- Low-dose MTX is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis as well as Crohn's disease.

بجرعات قليلة بنستخدمه بعلاج ال **inflammatory disease** لحاله
مثل ال **Rheumatoid arthritis and Crohn's disease**

Other Antifolate Drugs

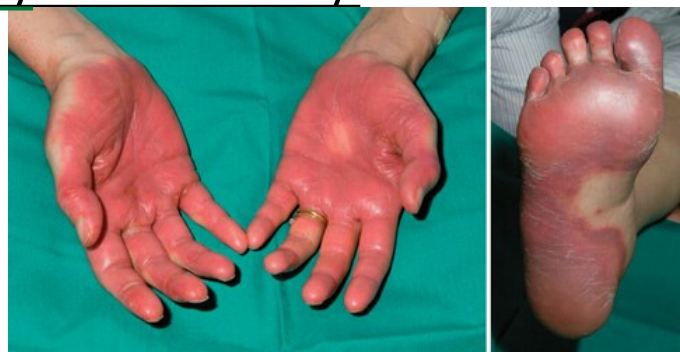
1. Pemetrexed

- Pemetrexed is an antifolate analog with activity in the S phase of the cell cycle. As in the case of MTX, it is transported into the cell via the reduced folate carrier and requires activation by FPGS to yield higher polyglutamate forms.
- While this agent targets DHFR and enzymes involved in de novo purine nucleotide biosynthesis, its main mechanism of action is inhibition of thymidylate synthase (TS).
- At present, this antifolate is approved for use:
  - in combination with cisplatin in the treatment of mesothelioma
  - as a single agent in the second-line therapy of NSCLC
  - in combination with cisplatin for the first-line treatment of NSCLC
  - and most recently, as maintenance therapy in patients with NSCLC whose disease has not progressed after four cycles of platinum-based chemotherapy.

Other Antifolate Drugs

1. Pemetrexed

- As with MTX, pemetrexed is mainly excreted in the urine, and dose modification is required in patients with renal dysfunction.
- The main adverse effects include myelosuppression, skin rash, mucositis, diarrhea, fatigue, and **hand-foot syndrome**.
- Of note, vitamin supplementation with folic acid and vitamin B_{12} appears to reduce the toxicities associated with pemetrexed, while not interfering with clinical efficacy.
- The hand-foot syndrome is manifested by painful erythema and swelling of the hands and feet, and dexamethasone treatment has been shown to be effective in reducing the incidence and severity of this toxicity.



بيشتغل نفس ال MTX تمامًا من ناحية ال mechanism of action وإنه بشتغل بال S phase
ال target إله هو DHFR and enzymes involved in purine nucleotide biosynthesis لهيك بنعتبر ال main mechanism of action إله هي inhibition of thymidylate synthase.
بصيرله excretion in the urine لهيك لازم ننتبه ونعدل الجرعة بحالة ال renal dysfunction
بالنسبة لل adverse effects إلّي بيعملها ححط عليهم هايلايتر وركزوا أكتر شي على ال hand- foot syndrome
لو أنا أعطيت لمريض بياخد هاد الدوا مع فوليك اسيد وفيتامين بي ١٢ ف هيك بكون قللت من ال toxicity of pemetrexed بدون ما نأثر ع فعاليته
طيب هاي ال hand- foot syndrome شو أعراضها ؟ painful erythema and swelling of the hand and feet وعلاجه هو ال dexamethasone

Other Antifolate Drugs

ما في إشي جديد كله نفس ما حكينا سابقًا بس ححط هايلايتر عالشي المميز فيه

2. Pralatrexate

- Pralatrexate is an antifolate analog, and as in the case of MTX, it is transported into the cell via the reduced folate carrier (RFC) and requires activation by FPGS to yield higher polyglutamate forms.
- It inhibits DHFR, inhibits enzymes involved in de novo purine nucleotide biosynthesis, and also inhibits TS.
- Although pralatrexate was originally developed for NSCLC, it is presently approved for use in the treatment of relapsed or refractory peripheral T-cell lymphoma.
- As with the other antifolate analogs, pralatrexate is mainly excreted in the urine, and dose modification is required in renal dysfunction.
- The main adverse effects include myelosuppression, skin rash, mucositis, diarrhea, and fatigue.
- Vitamin supplementation with folic acid and vitamin B_{12} appear to reduce the toxicities associated with pralatrexate, while not interfering with clinical efficacy.