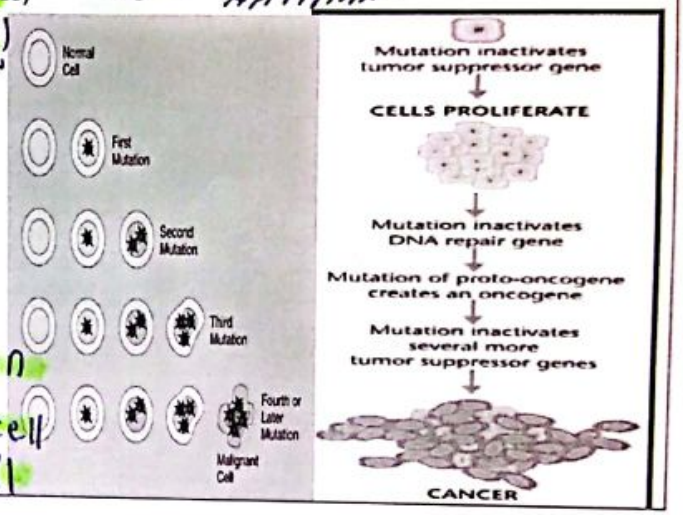
- Cancer arises from one single cell. The transformation from a normal cell into a tumour cell is a **multistage process.** تعريف
- Cancer cells are altered host cells: خصائص الخلايا السرطانية
  - ① shorter cell cycle (accelerated) دوره حياتها قصيره
  - ② excessive proliferation تتكاثر بشكل مفرط
  - ③ higher activity of nucleic acid and protein synthesis
  - ④ altered cell-cell communication تغيير الاتصالات بين الخلايا
  - ⑤ invasive (disrupt normal healthy tissues) تدمير الخلايا السليمة تغزوا
  - migration to distant sites (metastasis) تعريف الهجره الى مواقع بعيده



*

metastasis	multistage
migration to distant sites	transformation from normal cell to tumour cell

Treatment cancer

- 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 ① surgery, and/or ② radiotherapy, and/or ③ chemotherapy.
- The primary goal is to cure cancer and improving the patient's quality of life.

الممسوحة ضوئيا بـ CamScanner

الهاتأثير قاتل واماميت على الخلايا السرطانية

PRINCIPLES OF CANCER CHEMOTHERAPY

- Cause a lethal cytotoxic event or apoptosis in the cancer.
- Generally directed toward DNA ① or against metabolic sites ② essential to cell replication بتشتغل على
  - 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.

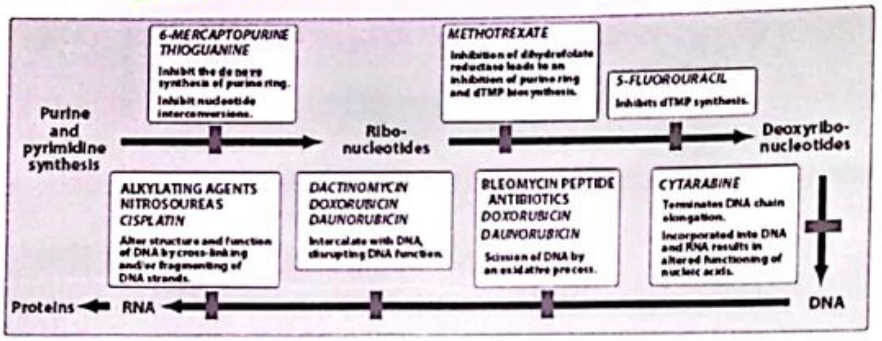


Figure 39.2
Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.

Chemotherapy لـ 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 ② of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life (palliative therapy). (تخفيفي)

الممسوحة ضوئيا بـ CamScanner

Treatment strategies

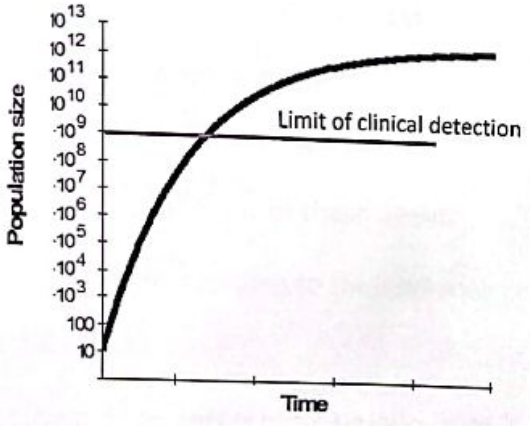
2. Chemotherapy is indicated when: -: متى يستخدم الـchemotherapy *

- Neoplasms are disseminated and are not amenable to surgery.
- Also used as a supplemental treatment to attack micrometastases ① following surgery and radiation treatment, (adjuvant chemotherapy). بعد العملية الجراحية
- ② Prior to the surgical procedure in an attempt to shrink the cancer (neoadjuvant chemotherapy) قبل العملية الجراحية
- ③ Also given in low doses to assist in prolonging a remission (maintenance chemotherapy).

Cell growth kinetics

- **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.

بطريقة



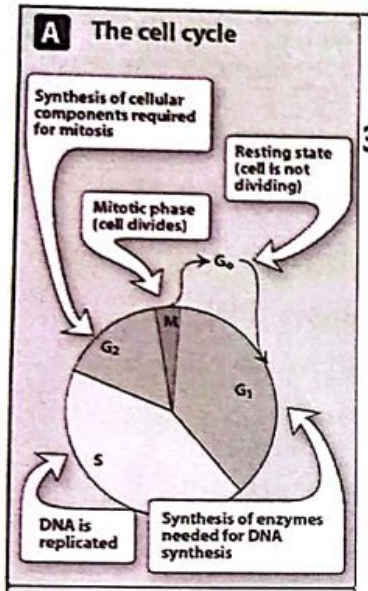
Gompertzian Growth Curve

الممسوحة ضوئيا بـ CamScanner

after clinical signs of cancer have disappeared.

organ toxicity.

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:

- 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

الممسوحة ضوئيا بـ CamScanner

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.

← القابلية للعلاج

الممسوحة ضوئيا بـ CamScanner

Treatment protocols

- **Drug combination** is more successful than single drug treatment in most cancers.
- The following principles are important for selecting appropriate drugs to use in combination chemotherapy: * شروط استخدام الـ combination

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

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

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

(4) The drugs should have different toxic effects

- The advantages of combinations: * فوائد استعمال الـ combination
  1. Provide maximal cell killing within the range of tolerated toxicity
  2. Effective against a broader range of cell lines in the heterogeneous tumor population
  3. 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

الممسوحة ضوئيا بـ CamScanner

* chemotherapy dosing depend on : → body weight
→ AUC
→ BSA → (most used)

بسبب
مقارنة دقيقة
provides an accurate comparison of activity and toxicity

correlates with cardiac output العلاقة

Determine renal and hepatic blood flow, thus affects drug elimination.

* في الـ chemotherapy : بحتاج انه dose adjustment ←

في حاله الـ renal and Kidney dysfunction

Problems associated with chemotherapy

* كيف الخلايا السرطانيه بتعمل resistance على ادويه الcancer

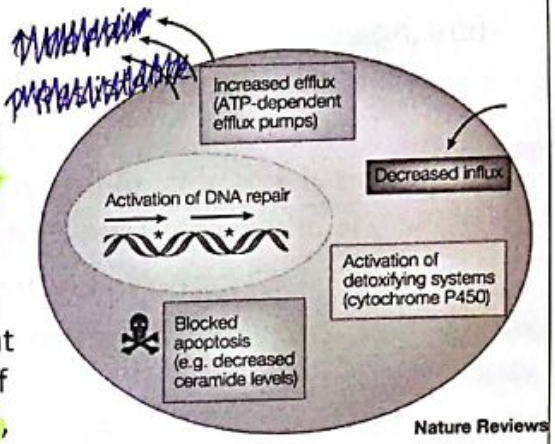
A. Resistance:

- 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.

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.

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—Increased 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).

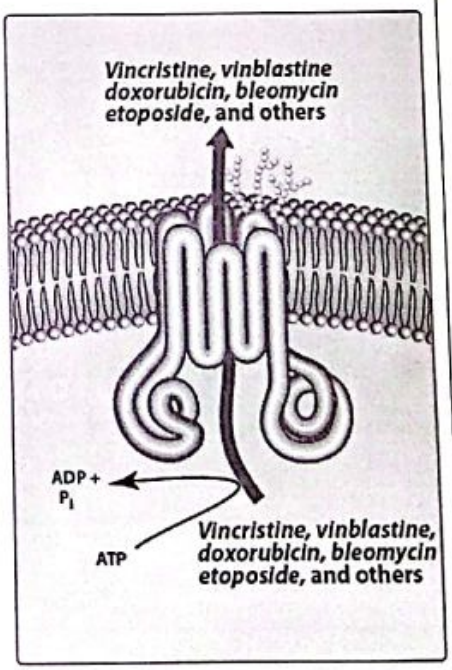


Figure 39.5
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

الممسوحة ضوئيا بـ CamScanner

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:
  1. Cytoprotectant drugs as prostaglandins to protect the GIT from ulcer
     - Perfusing the tumor locally
  2. Removing some of the patient's marrow prior to intensive treatment and then reimplanting it.
  3. Promoting intensive diuresis to prevent bladder toxicities.
  4. The megaloblastic anemia that occurs with methotrexate can be effectively counteracted by administering folinic acid (leucovorin, 5-formyltetrahydrofolic acid)

folinic acid اعطي الريفن

Antimetabolites

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

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

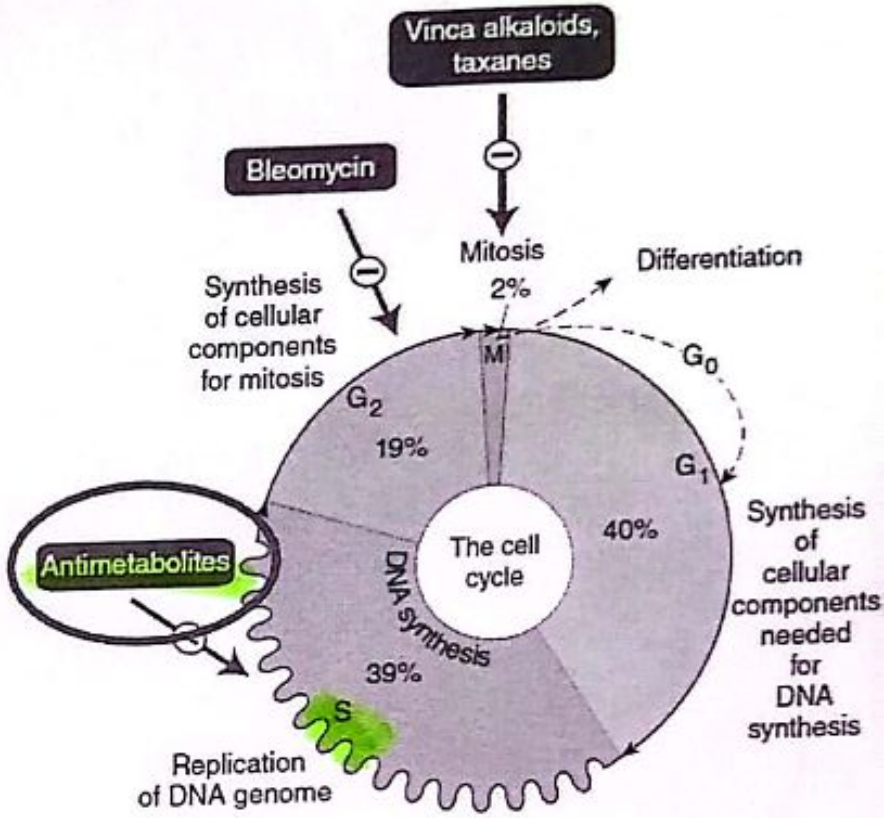


FIGURE 54–1 Phases of the cell cycle that are susceptible to the actions of cell cycle-specific (CCS) drugs. All dividing cells—normal and neoplastic—must traverse these cell cycle phases before and during cell division. Tumor cells are usually most responsive to specific drugs (or drug groups) in the 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.)

CamScanner المسوحة ضوئيا بـ

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.

Organization of folate forms and their role in one-

الممسوحة ضوئيا بـ CamScanner

- Methotrexate inter the cell via → reduced folate carrier

Methotrexate —(reduced folate carrier)→ inter the cell

- Methotrexate (inactive) —(folylpolyglutamate synthase (FPGS))→ polyglutamate metabolites (active form)
داخل الخلية

CamScanner الممسوحة ضوئيا

Methotrexate Resistance

tance عنا 5 طرق صعمل فيها الخليه السرطانيه * للـ MTX :-

- Several resistance mechanisms to MTX have been identified, and they include:

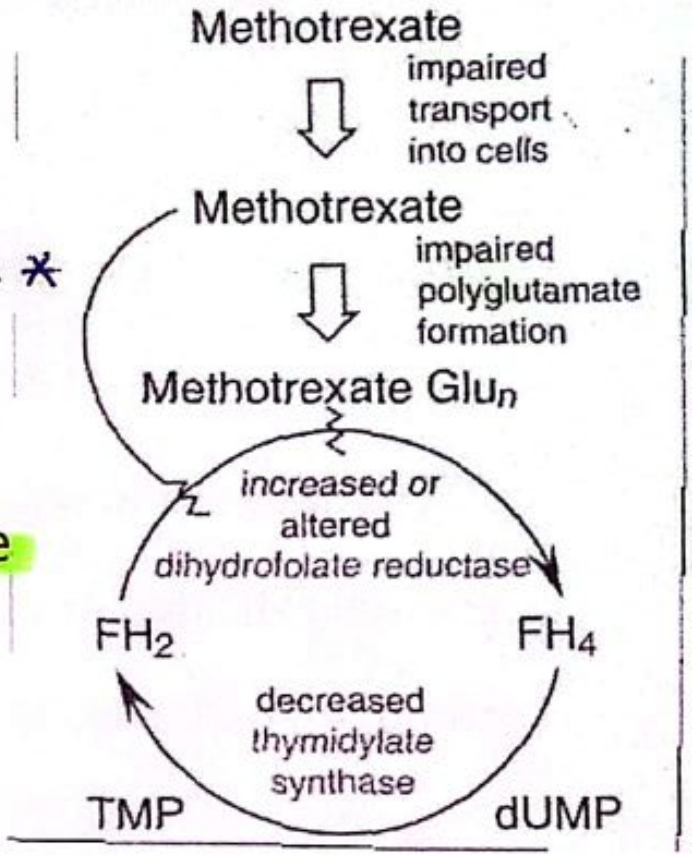
  (1) decreased drug transport via the reduced folate carrier or folate receptor protein

  (2) decreased formation of cytotoxic MTX polyglutamates,

  (3) increased levels of the target enzyme DHFR through gene amplification and other genetic mechanisms

  (4) altered DHFR protein with reduced affinity for MTX.

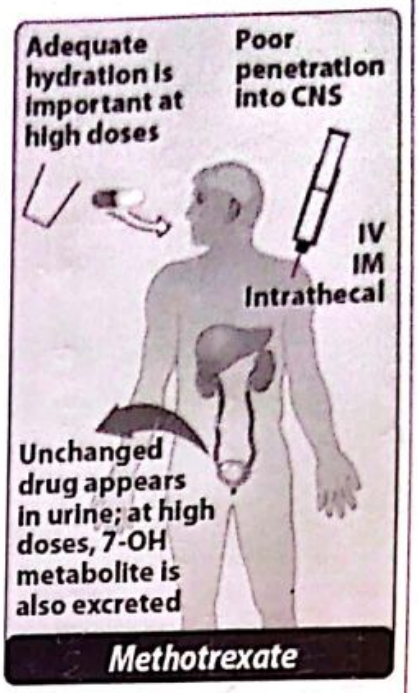
  (5) decreased accumulation of drug through activation of the multidrug resistance transporter P170 glycoprotein.



الممسوحة ضوئيا بـ CamScanner

Pharmacokinetics of MTX

- MTX is administered by the intravenous (IV), intrathecal, or oral route. However, oral bioavailability is saturable and erratic at doses greater than 25 mg/m².
- **Renal excretion** is the main route of elimination and is mediated by glomerular filtration (kidney) 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 (1) and the patient well hydrated (3) to avoid renal toxicity.



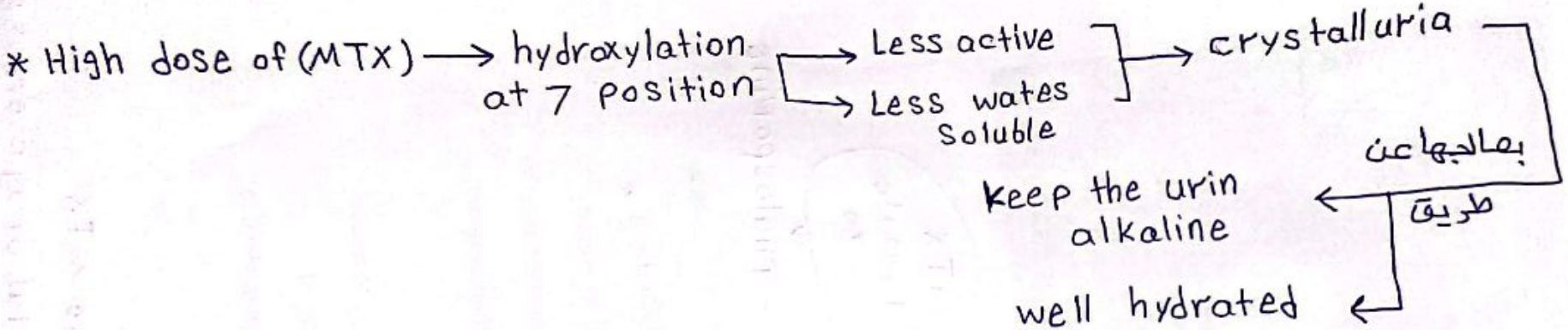
penicillin
aspirin
MTX ما بصير اخذه مع
NSAIDs
cephalosporins

Adverse effects of MTX

- Nausea, vomiting, and diarrhea, stomatitis, myelosuppression with neutropenia and thrombocytopenia. (mainly folic acid deficiency) * يعمل بعض اعراض ال
- 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.
- 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.
- Contraindications: It should be avoided in pregnancy. (MTX)

* leucovorin used for → high-dose MTX
→ accidental drug overdose

الممسوحة ضوئيا بـ CamScanner



الممسوحة ضوئيا بـ CamScanner

Other Antifolate Drugs

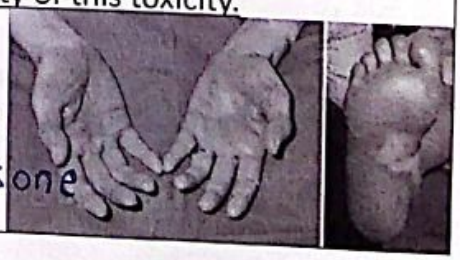
1. Pemetrexed

- 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.



* hand-foot syndrome = يعالجها عن طريق dexamethasone

* pemetrexed + folic acid + vitamin B12 = reduce toxicity pemetrexed

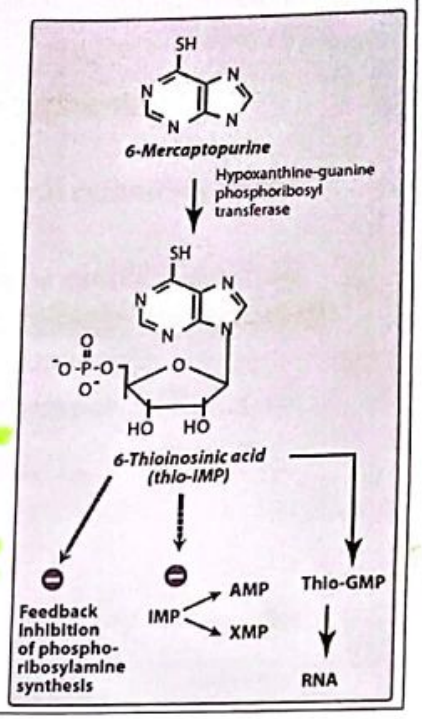
الممسوحة ضوئيا بـ CamScanner

Purine antagonists

6-Mercaptopurine (6-MP) → prodrug

Mechanism of action: inactive

- **6-Mercaptopurine (6-MP)** was the first of the thiopurine analogs found to be effective in cancer therapy.
- This agent is used in the treatment of AML (acute myelogenous leukemia).
- 6-MP is inactive in its parent form and must be metabolized **by hypoxanthine-guanine phosphoribosyl transferase (HGPRT)** to form the monophosphate nucleotide 6-thioinosinic acid **(thio-IMP)**, which in turn inhibits several enzymes of de novo purine nucleotide synthesis. (active form)
- The monophosphate form is eventually metabolized to the triphosphate form, which can then be incorporated into both RNA and DNA. (nonfunctional RNA and DNA).



6-MP

Resistance:

1. ↓ Decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome)
2. ↑ Increased dephosphorylation, Increased metabolism of the drug to thiouric acid.

Pharmacokinetics: orally * مابصير اعطيه

- Absorption by the oral route is erratic and incomplete.
- The bioavailability of 6-MP can be reduced by the first-pass metabolism in the liver
- 6-MP is converted to an inactive metabolite (6-thiouric acid) by an oxidation reaction catalyzed by xanthine oxidase.
- This is an important issue because the purine analog **allopurinol, a potent xanthine oxidase inhibitor,** is frequently used as a supportive care measure in the treatment of acute leukemias to prevent the development of hyperuricemia that often occurs with tumor cell lysis. Because allopurinol inhibits xanthine oxidase, simultaneous therapy with allopurinol and 6-MP would result in increased levels of 6-MP, thereby leading to excessive toxicity. In this setting, the dose of mercaptopurine must be reduced by 50–75%.
- The parent drug and its metabolites are excreted by the kidney.

Adverse effects:

- Myelosuppression, immunosuppression, and hepatotoxicity.

(xanthine oxidase inhibitor) allopurinol والـ 6-MP * بقدر اجمع بينهم

← عن طريق اني اقلل الجرعة

الممسوحة ضوئيا بـ CamScanner

Other Purine Antagonists

6-Thioguanine (6-TG)

- **6-TG** also inhibits several enzymes in the de novo purine **nucleotide** biosynthetic pathway.
- 6-TG has a synergistic action when used together with cytarabine in the treatment of adult acute leukemia.
- 6-TG is metabolized by deamination (not oxidation by xanthine oxidase). This is an important issue because 6-TG does not interact with allopurinol such as 6-MP. 6-TG can be used in full doses with allopurinol.
- The side effect profile is similar to 6-MP (myelosuppression, immunosuppression, and hepatotoxicity).

↓ لهياء
بعطيه جرعه كامله

* S/E انه نفس الـ 6-MP

Other Purine Antagonists

Fludarabine

- This purine nucleotide analog is used mainly in the treatment of low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL).
- It is given parenterally, and up to 25–30% of parent drug is excreted in the urine.
- The main dose-limiting toxicity is myelosuppression.
- This agent is a potent **immunosuppressant** with inhibitory effects on CD4 and CD8 T cells. Patients are at increased risk for opportunistic infections, including fungi, herpes, and *Pneumocystis jiroveci* pneumonia (PCP). Patients should receive PCP prophylaxis with trimethoprim-sulfamethoxazole (double strength) at least three times a week, and this should continue for up to 1 year after stopping fludarabine therapy.

* after stopping fludarabine therapy:-

patient should receive = (PCP) Prophylaxis
+
trimethoprim sulfamethoxazol

الممسوحة ضوئيا بـ CamScanner

Other Purine Antagonists

Cladribine

- Cladribine is indicated for the treatment of hairy cell leukemia, with activity in other low-grade lymphoid malignancies such as CLL and low-grade non-Hodgkin's lymphoma.
- It is normally administered as a single continuous 7-day infusion; under these conditions, it has a very manageable safety profile with the main toxicity consisting of transient myelosuppression. (1)
- As with other purine nucleoside analogs, it has immunosuppressive (2) effects, and a decrease in CD4 and CD8 T cells, lasting for over 1 year, is observed in patients.

الممسوحة ضوئيا بـ CamScanner

5-FU → prodrug

Clinical uses:

- 5-FU remains the most widely used agent in the treatment of colorectal cancer, both as adjuvant therapy and for advanced disease.
- It also has activity against a wide variety of solid tumors, including cancers of the breast, stomach, pancreas, esophagus, liver, head and neck, and anus.

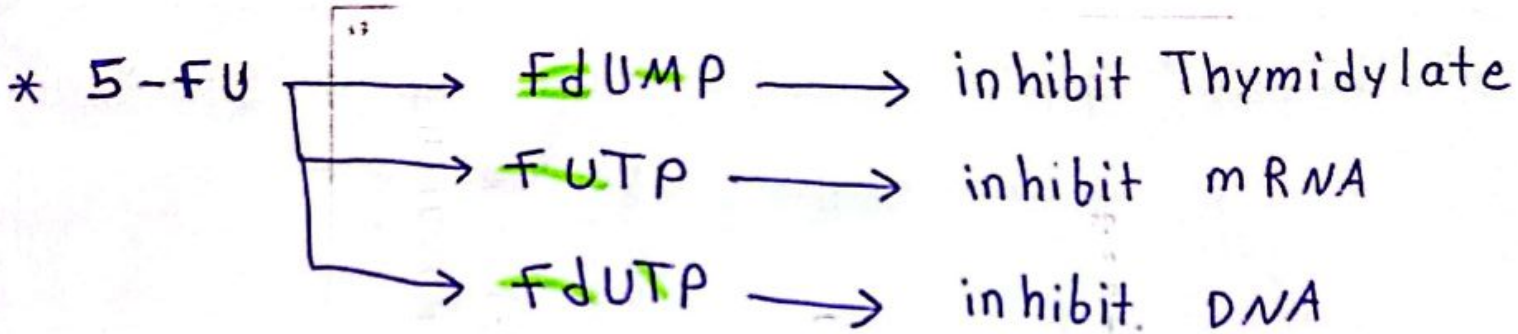
Side Effects:

* اله اعراض جانبية على
Skin + GI + neurons

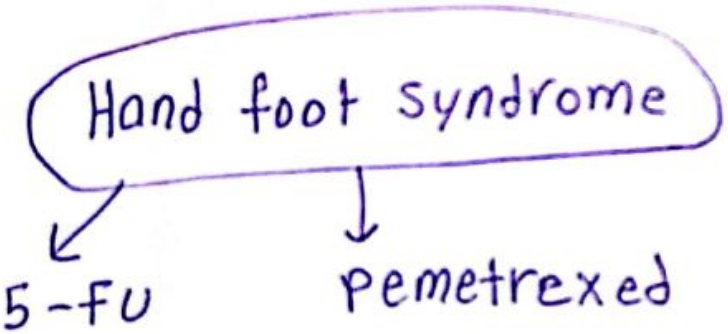
- Major toxicities include:

1. Myelosuppression
2. Gastrointestinal toxicity in the form of mucositis and diarrhea
3. Skin toxicity manifested by the hand-foot syndrome
4. Neurotoxicity.

الممسوحة ضوئيا بـ CamScanner



combination effect ← 5-FU *
on DNA + RNA



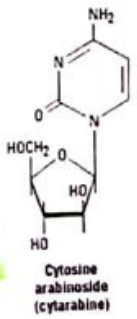
CamScanner المسوحة ضوئيا

5-FU

Pharmacokinetics:

- 5-FU is administered intravenously. Because of its extremely short half-life, on the order of 10–15 minutes, infusional schedules of administration have been generally favored over bolus schedules.
- Up to 80–85% of an administered dose of 5-FU is **catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD).** Of note, a pharmacogenetic syndrome involving partial or complete deficiency of the DPD enzyme is seen in up to 5% of cancer patients. In this particular setting, severe toxicity in the form of myelosuppression, diarrhea, nausea and vomiting, and neurotoxicity is observed.
- Although mutations in DPD can be identified in peripheral blood mononuclear cells, nearly 50% of patients who exhibit severe 5-FU toxicity do not have a defined mutation in the *DPD* gene. In addition, such mutations may not result in reduced expression of the DPD protein or in altered enzymatic activity. For this reason, genetic testing is not recommended at this time as part of routine clinical practice.

Other pyrimidine antagonists
Cytarabine



Cytosine arabinoside (cytarabine)

Mechanism of action:

- **Cytarabine (ara-C)** is converted by deoxycytidine kinase to the 5′-mononucleotide (ara-CMP). Ara-CMP is further metabolized to the diphosphate and triphosphate metabolites, **ara-CTP is the main cytotoxic metabolite**.
- Ara-CTP:

1. competitively inhibits DNA polymerase-α and DNA polymerase-β, thereby resulting in blockade of DNA synthesis and DNA repair, respectively.
2. is also incorporated into RNA and DNA. Incorporation into DNA leads to interference with chain elongation.

الممسوحة ضوئيا بـ CamScanner

Clinical uses:

- The clinical activity of cytarabine is highly schedule-dependent and because of its rapid degradation, it is usually administered via continuous infusion over a 5–7 day period.
- Its activity is limited exclusively to hematologic malignancies, including acute myelogenous leukemia and non-Hodgkin's lymphoma.
- This agent has absolutely no activity in solid tumors.

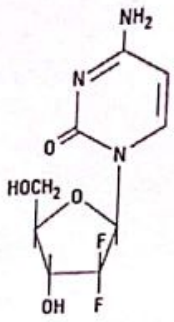
Side Effects: (ara-C)

- The main adverse effects associated with cytarabine therapy include myelosuppression, mucositis, nausea and vomiting, and neurotoxicity when high-dose therapy is administered.

الممسوحة ضوئيا بـ CamScanner

Other pyrimidine antagonists

Gemcitabine



Gemcitabine

Mechanism of action:

- **Gemcitabine** is a fluorine-substituted deoxycytidine analog that is phosphorylated initially by the enzyme deoxycytidine kinase to the monophosphate form and then by other nucleoside kinases to the diphosphate and triphosphate nucleotide forms.
- The antitumor effect is considered to result from several mechanisms:

1. inhibition by gemcitabine triphosphate of DNA polymerase-α and DNA polymerase-β, thereby resulting in blockade of DNA synthesis and DNA repair
2. incorporation of gemcitabine triphosphate into DNA, resulting in chain termination.
3. inhibition of ribonucleotide reductase by gemcitabine diphosphate, which reduces the level of deoxyribonucleoside triphosphates required for DNA synthesis

Other pyrimidine antagonists

Gemcitabine

Clinical uses:

- In contrast to cytarabine, which is inactive in solid tumors, **gemcitabine** has broad-spectrum activity against solid tumors and hematologic malignancies. This nucleoside analog was initially approved for use in advanced pancreatic cancer but is now widely used to treat a broad range of malignancies, including NSCLC, bladder cancer, ovarian cancer, soft tissue sarcoma, and non-Hodgkin's lymphoma.

Side Effects:

1. Myelosuppression in the form of neutropenia is the principal dose-limiting toxicity.
2. Nausea and vomiting occur in 70% of patients
3. a flu-like syndrome has also been observed.

الممسوحة ضوئيا بـ CamScanner