Medical Committee
The University of Jordan

PHARMACOLOGY

Slide # : 15- Anticancer

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SHEET

SLIDES

DONE BY: ISSA KHASHAN

Cancer treatment

- There are three major approaches to the treatment of the common solid tumours:
- SURGERY
- RADIOTHERAPY
- CHEMOTHERAPY

The primary tumour is removed by surgery. If it has not metastasised then the surgery may prove curative.

- Radiotherapy, irradiation with high energy X-rays (4 to 25 MeV), may be applied subsequent to surgery to help prevent re-growth of the primary tumour.

- Surgery plus radiotherapy is a common treatment modality.

- **X-rays kill tumour cells (and healthy normal cells in division) by free radical damage to DNA that results in double strand breaks which are lethal to cells at mitosis.**

- **Tumours that are not resectable may be treated by radiotherapy alone, in which the treatment is largely palliative.**

- **Most of the 50% cure is effected by surgery and radiotherapy on non-metastatic tumours.**

- **If the disease is found to be metastatic then systemic chemotherapy is administered after surgery and radiotherapy.**

Cancer Chemotherapy

- **Cancer drugs are not specific for cancer cells but are cytotoxic to all proliferating cells in cycle.**
- **Their major unwanted toxicity is damage to bone marrow function and to the epithelial lining of the gut.**
- **Generally speaking, these are the dose-limiting toxicities.**
- **Nausea and vomiting may also be serious side-effects which are now well-controlled by 5-HT_3 antagonists (Ondansetron).**

Cocktail

- **Drugs are administered as a cocktail of three or more components at the maximum dose that can be tolerated by the bone marrow.**

- **The cocktail is administered once a day by IV injection/infusion for a week,**

- **the patient's haemopoietic system permitted to re-populate for three weeks and the process repeated up to half a dozen times.**

Cocktail

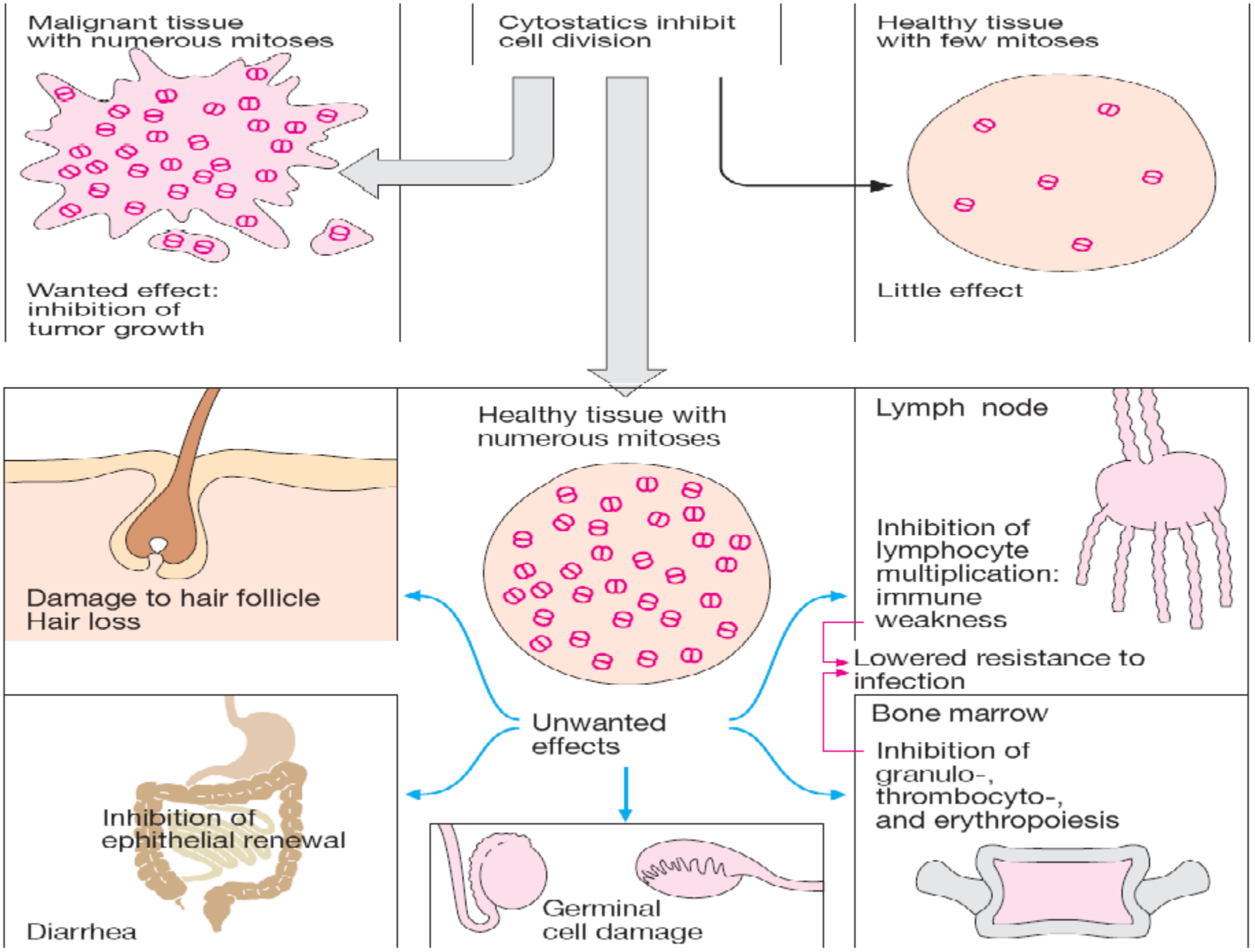
- **The therapeutic cocktail comprises drugs whose**

(1) Mechanism of action differ, the intention being

a. Additive or synergistic effect

b. to delay the appearance of drug-resistant cells for as long as possible.

(2) Major toxicity differ, non overlapping toxicity.


Malignant tissue with numerous mitoses
Cytostatics inhibit cell division
Healthy tissue with few mitoses
Wanted effect: inhibition of tumor growth
Little effect
Damage to hair follicle
Hair loss
Healthy tissue with numerous mitoses
Lymph node
Inhibition of lymphocyte multiplication: immune weakness
Lowered resistance to infection
Unwanted effects
Bone marrow
Inhibition of granulo-, thrombocyto-, and erythropoiesis
Inhibition of ephithelial renewal
Diarrhea
Germinal cell damage

CANCER DRUG CLASSES

- The classes of drugs currently used in the cancer clinic are

1. DNA Binding Agents (intercalating and alkylating agents)

2. Mitotic Spindle Inhibitors (modulators of tubulin polymerisation)

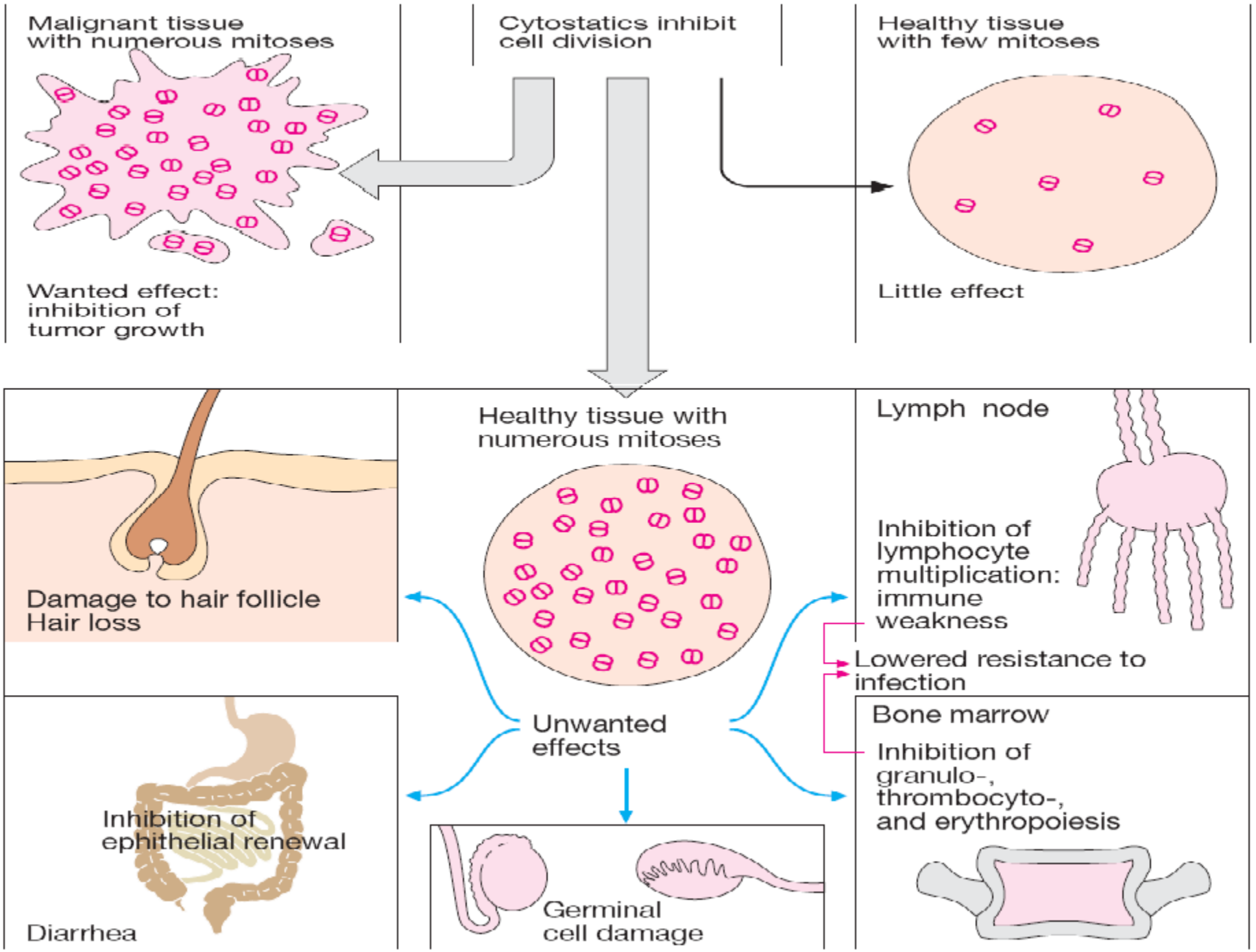
3. Antimetabolites (anti-folates, pyrimidine and purine analogues)

4. Hormones and Hormone Antagonists

5. Miscellaneous anticancer drugs

Anti-cancer drugs

Subclass	Prototype	Major Variants	Other Significant Agents
Alkylating agents			
Nitrogen mustards	Mechlorethamine		Cyclophosphamide, chlorambucil
Nitrosoureas	Carmustine	Lomustine	
Alkylsulfonates	Busulfan		
Platinum complex	Cisplatin	Carboplatin	
Triazenes	Dacarbazine		
Hydrazines	Procarbazine		
Antimetabolites			
Folate analogs	Methotrexate		
Purine analogs	Mercaptopurine		Thioguanine
Pyrimidine analogs	Fluorouracil		Cytarabine
Plant alkaloids			
Vinca alkaloids	Vinblastine	Vincristine	
Podophyllotoxins	Etoposide	Teniposide	
Other	Paclitaxel		Docetaxel
Antibiotics			
Anthracyclines	Doxorubicin	Daunorubicin	
Bleomycins	Bleomycin		
Actinomycins	Dactinomycin		
Mitomycins	Mitomycin		
Hormones			
Adrenocorticoids	Prednisone	Hydrocortisone	
Androgens	Testosterone	Fluoxymesterone	
Estrogens	Diethylstilbestrol	Ethinyl estradiol	
Progestins	Hydroxyprogesterone	Medroxyprogesterone	
Antiestrogens			
Receptor blockers	Tamoxifen	Toremifene	
Aromatase inhibitors	Anastrozole	Letrozole	
Antiandrogens	Flutamide		
Gonadotropin-releasing hormone agonists	Leuprolide	Goserelin, naferelin	
Monoclonal antibodies	Rituximab trastuzumab		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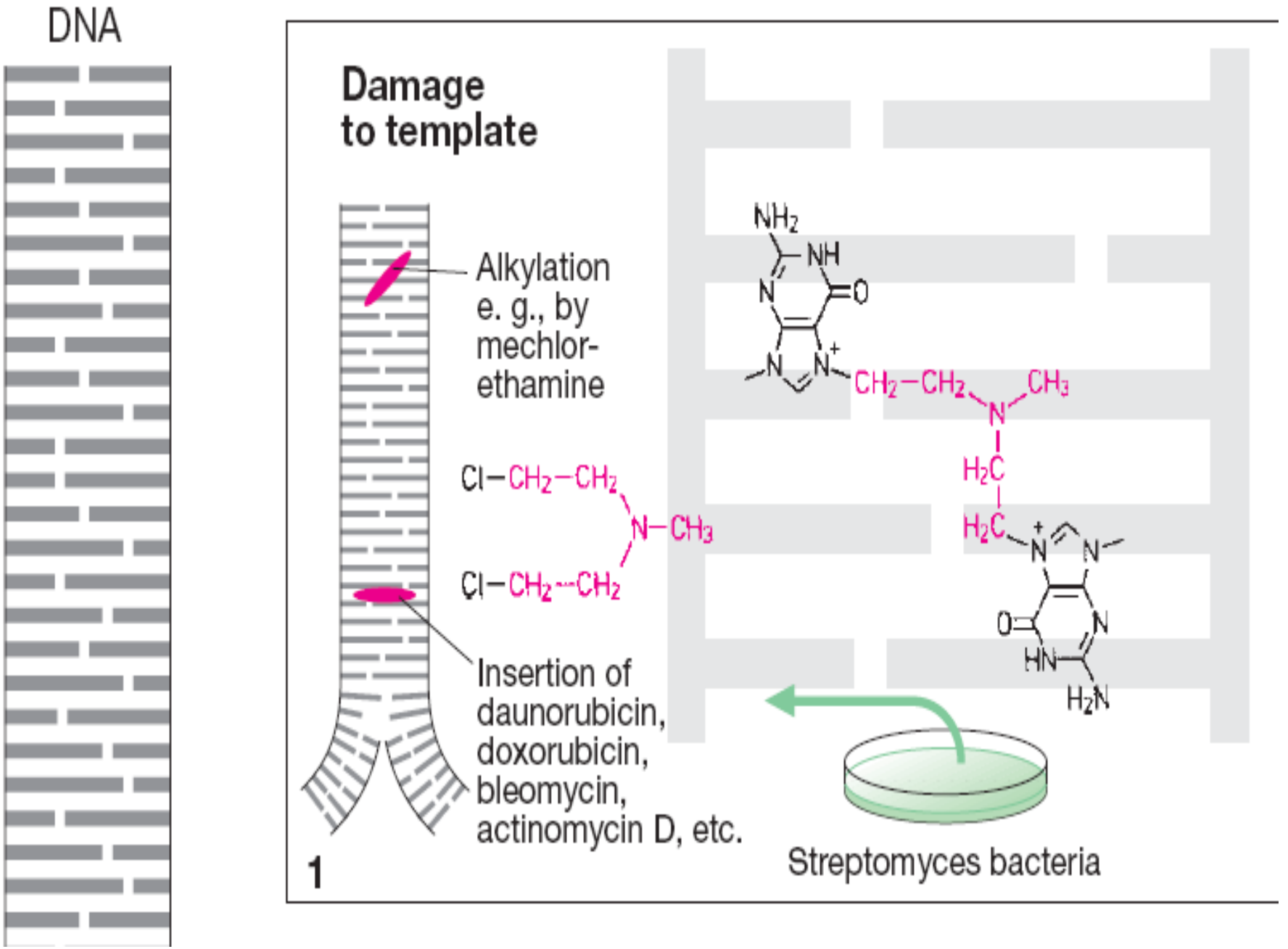
Diarrhea
Germinal cell damage

DNA binding agents
Intercalating agents

- **Intercalating agents are flat planar aromatic compounds that insert themselves in between the DNA basepairs.**

- **They either inhibit RNA polymerase activity but not DNA polymerase or exert their action as cancer drugs by poison the activity of topoisomerase II.**

- **Clinically used intercalating agents include ANTHRACYCLINES , MITOXANTRONE, ACTINOMYCIN D and Bleomycin**


DNA
Damage to template
Alkylation e. g., by mechlor-ethamine
Cl–CH2–CH2
N–CH3
Cl–CH2–CH2
Insertion of daunorubicin, doxorubicin, bleomycin, actinomycin D, etc.
1
NH2
NH
N
O
N
N+
CH2–CH2
N
CH3
H2C
H2C
N+
N
O
N
HN
H2N
Streptomyces bacteria

Anthracyclines

- **are the most commonly used anticancer drug,**
- **Doxorubicin (adriamycin) having activity against a wide range of solid tumours. (Most common drug)**
- **Daunorubicin (daunomycin) being used against acute myeloid leukemia (AML)**
- **Idarubicin is a semisynthetic anthracycline that took Daunorubicin place in AML therapy.**
- **Epirubicin is a doxorubicin analogue used in metastatic breast cancer and gastric cancer**

Anthracyclines

- **DNA strand scission via effects on Top II enzyme (topoisomerase poisons)**
- **High-affinity binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis.**
- **Binding to membranes and altering fluidity**
- **Generation of the free radical and oxygen radicals**

Anthracyclin

- **Their main toxicities are**

  - Bone marrow depression

  - Total alopecia

- **BUT the anthracyclines have a strange dose-limiting irreversible and lethal cardiomyopathy.**

- **This cardiotoxicity may be a result of the generation of free radicals and lipid peroxidase.**

HOW TO REDUCE THIS ..... Dexrazoxane

Bleomycin

bleomycin intercalates DNA, the major cytotoxicity is believed to result from iron catalyzed free radical formation and DNA strand breakage.

- **It is useful in Hodgkin's and non-Hodgkin's lymphomas, testicular cancer, and several other solid tumors.**

Adverse Effects:

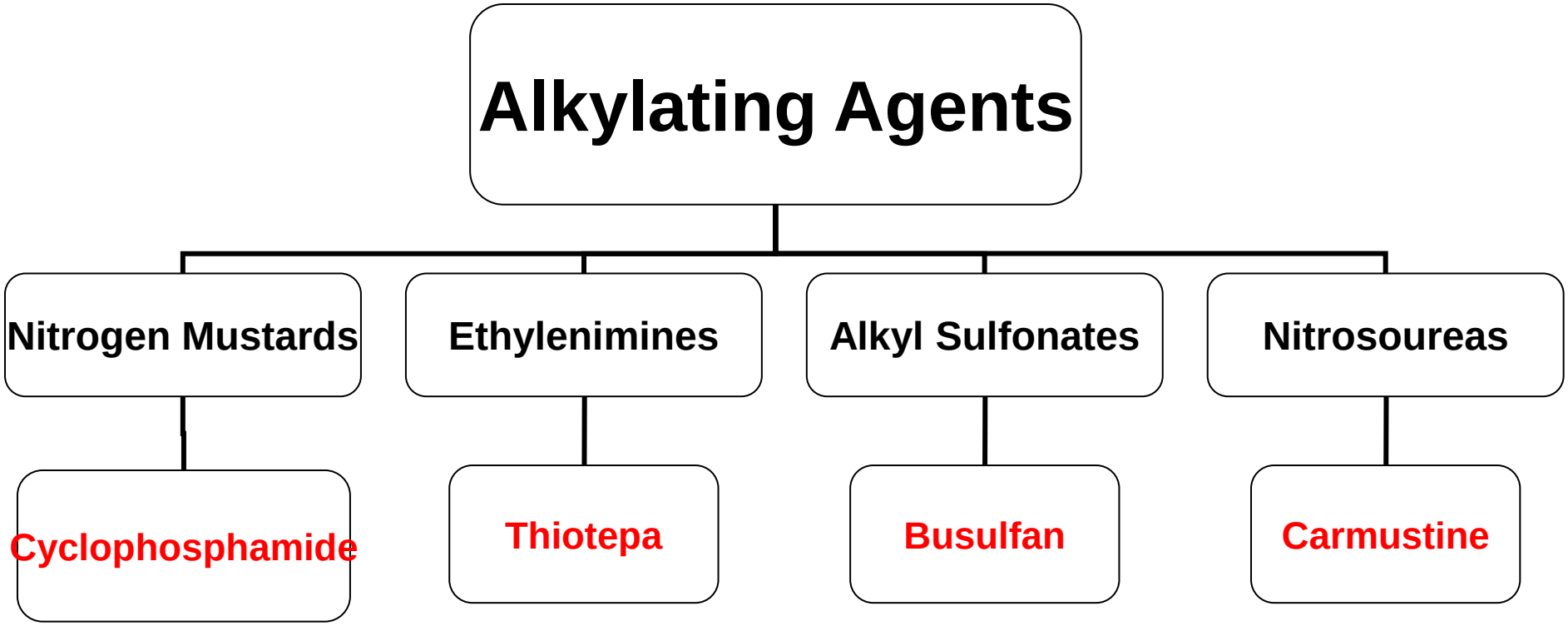
- **Bleomycin produces very little myelosuppression.**

- **The most serious toxicities of Bleomycin are pulmonary and mucocutaneous reactions.**

Distinctive Toxicities of Some Anticancer Drugs

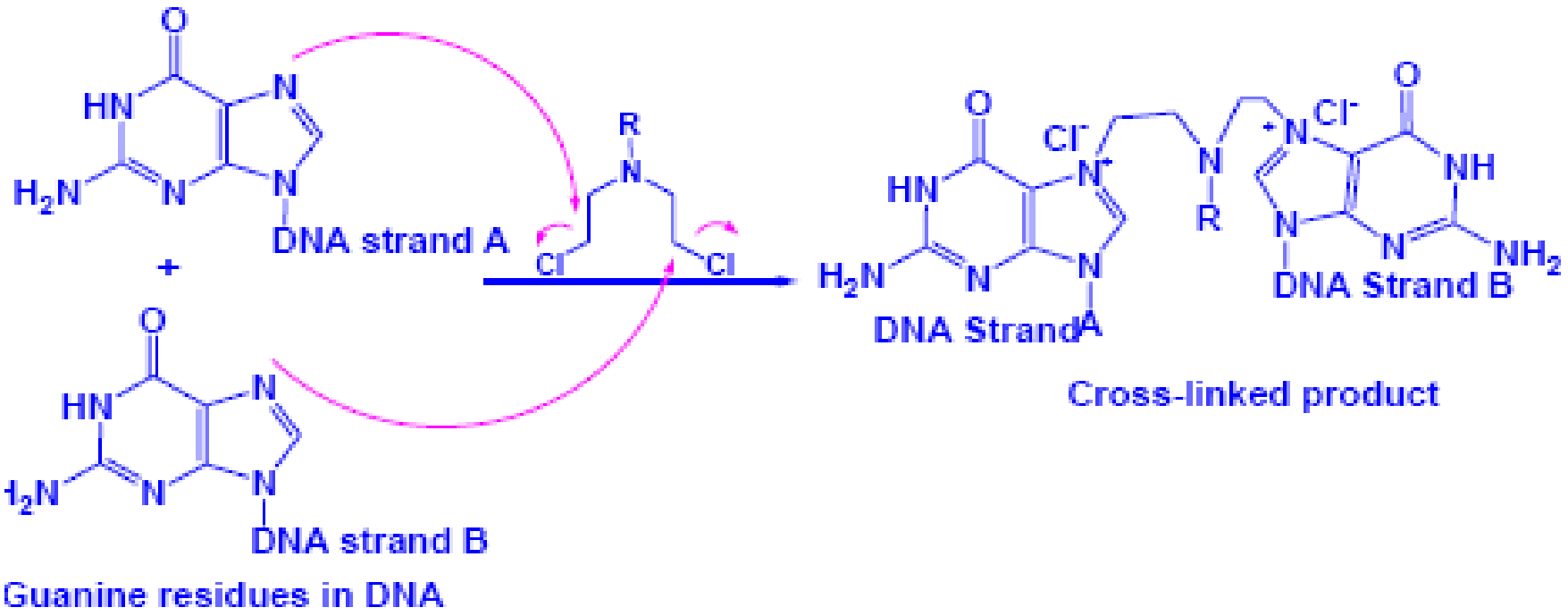
Toxicity	Drug(s)
Renal	Cisplatin,* methotrexate
Hepatic	6-MP, busulfan, cyclophosphamide
Pulmonary	Bleomycin,* busulfan, procarbazine
Cardiac	Doxorubicin, daunorubicin
Neurologic	Vincristine,* cisplatin, paclitaxel
Immunosuppressive	Cyclophosphamide, cytarabine, dactinomycin, methotrexate
Other	Cyclophosphamide (hemorrhagic cystitis); procarbazine (leukemia); asparaginase* (pancreatitis)

*Less Bone marrow suppression – "marrow sparing"


Alkylating Agents
Nitrogen Mustards
Ethylenimines
Alkyl Sulfonates
Nitrosoureas
Cyclophosphamide
Thiotepa
Busulfan
Carmustine

ALKYLATING AGENTS

- **Alkylating agents bind irreversibly to DNA and function by crosslinking the two Watson-Crick strands, thereby inhibiting strand separation and preventing DNA replication.**



Nitrogen mustards

- **Cyclophosphamide (oral)**
- **Ifosfamide**
- **Melphalan (oral)**
- **Chlorambucil (oral) least toxic**

Nitrogen mustards

cyclophosphamide

1. **most commonly used alkylating agent**

   used in lymphomas, leukemias, sarcomas, carcinomas of breast or ovary, as well as childhood malignancies.

2. **has a special place in the maintenance therapy for breast cancer.**

3. **It is also a potent immunosuppressant,**

   it is used in the management of rheumatoid disorders and autoimmune nephritis.

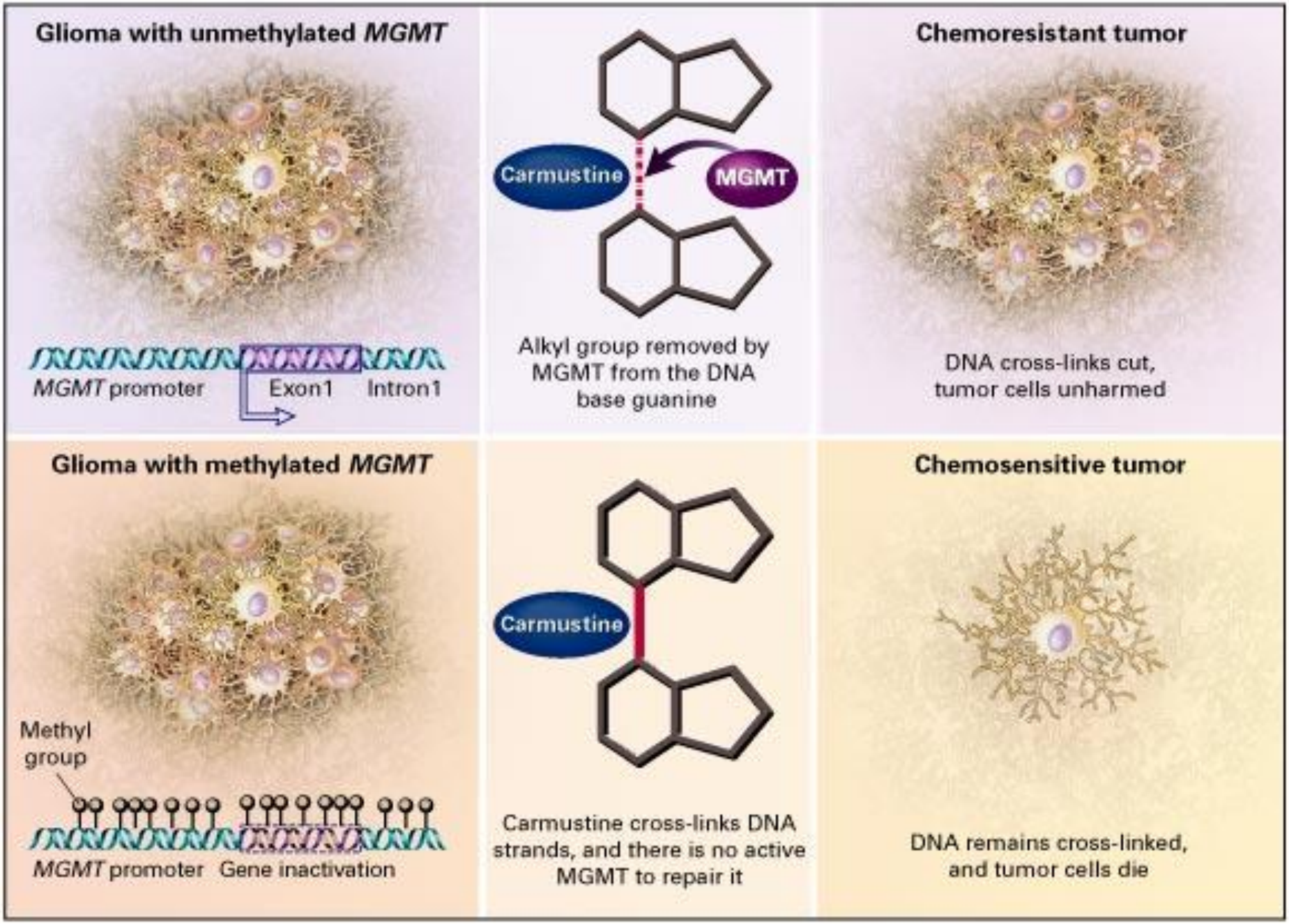
4. **Cystitis (inflammation of the urinary bladder) may result.**

   co-administered with N-acetylcystein or 2-mercaptoethanesulfonate (mesna). Both are thiols that neutralized acrolein

Nitrosoureas

- **The best known clinical agents are CARMUSTINE and LOMUSTINE (oral).**
- **The nitrosoureas pass the blood-brain barrier and are active against brain tumours.**
- **These drugs appear to be non-cross-resistant with other alkylating agents.**
- **Streptozocin (minimal bone marrow toxicity)**

  used to treat insulin-secreting islet cell carcinoma of the pancreas


Glioma with unmethylated *MGMT*
MGMT promoter
Exon1
Intron1
Carmustine
MGMT
Alkyl group removed by MGMT from the DNA base guanine
Chemoresistant tumor
DNA cross-links cut, tumor cells unharmed
Glioma with methylated *MGMT*
Methyl group
MGMT promoter
Gene inactivation
Carmustine
Carmustine cross-links DNA strands, and there is no active MGMT to repair it
Chemosensitive tumor
DNA remains cross-linked, and tumor cells die

Platinum analogs

- **In the clinic, cisplatin behaves very similarly to the organic alkylating agents and finds widespread use.**
- **Cisplatin has efficacy against a wide range of neoplasms.**
- **It is particularly effective in germ cell tumours (testicular cancer and ovarian tumours) and in breast cancer.**
- **Its use in combination chemotherapy has revolutionised the treatment of testicular and ovarian tumours, frequently leading to complete cure of testicular cancers in young men.**

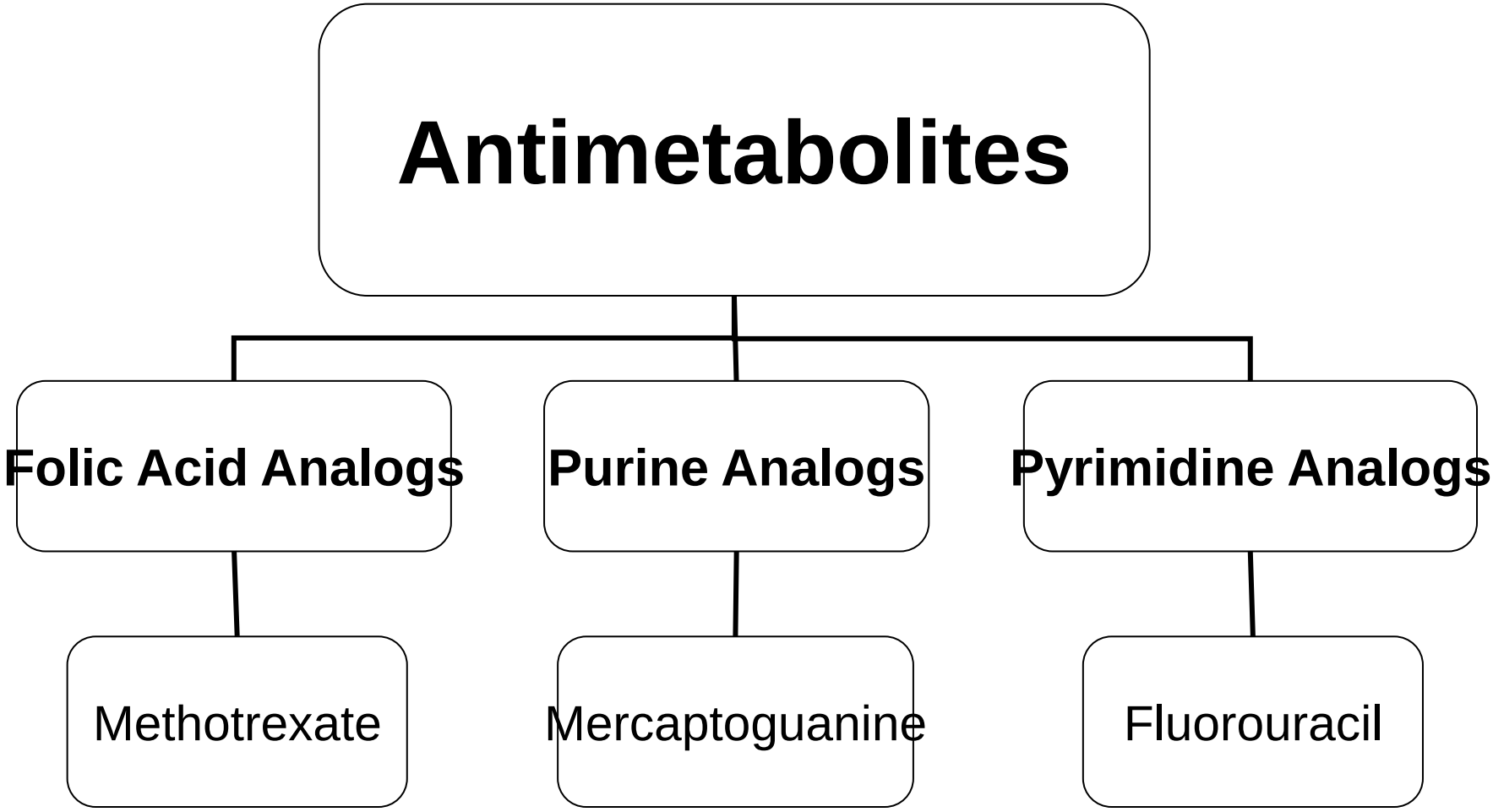
Platinum analogs

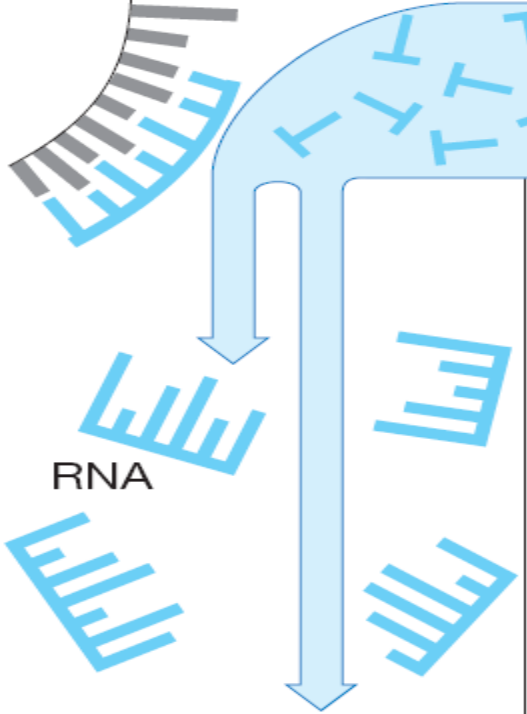
- **Its main toxicities are to the kidney and to the ear,**
- **produces relatively little myelosuppression but can cause severe nausea, vomiting.**
- **Carboplatin is a second generation platinum analog that has less renal toxicity and gastrointestinal toxicity.**
- **Though Carboplatin has widely replace cisplatin in chemotherapeutic regimen.**

ERCC1 mRNA or protein expression levels correlate with cisplatin resistance in human cancer cell lines

Cancer cell lines	ERCC1 expression	Phenotypic effets
ovarian	mRNA (3-fold ↑)	Cisplatine resistance
ovarian	mRNA and protein (2-fold ↓)	↓ Repair of cisplatin-DNA adducts
ovarian	ERCC1 anti-sense mRNA	Restored sensitivity to cisplatine
ovarian	ERCC1 SiRNA	↑ > 53-fold in cisplatin sensitivity
cervical	mRNA	Positively correlated with oxaloplatine resistance
testis	protein	Low levels of ERCC1 compared with other cell lines
lung	ERCC1 anti-sense mRNA	Decreased the repair capacity

Gossage et al, Cancer Treat Rev. 2007


Antimetabolites
Folic Acid Analogs
Purine Analogs
Pyrimidine Analogs
Methotrexate
Mercaptoguanine
Fluorouracil



Inhibition of nucleotide synthesi

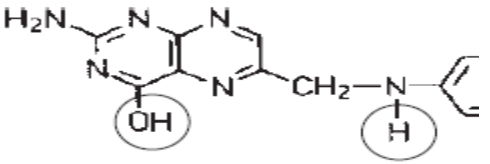
Purines

Thymine Nucleotide

Tetrahydro-folate

Dihydrofolate Reductase

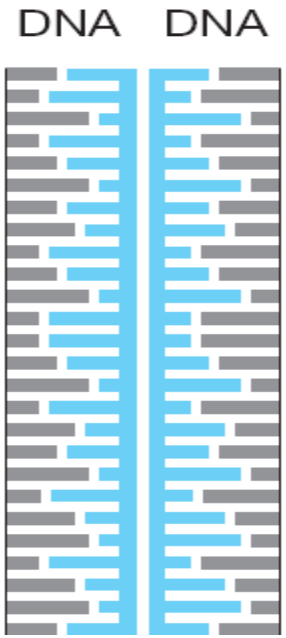
Folic acid



Inhibition by

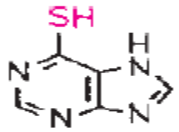
Aminopterin
Methotrexate

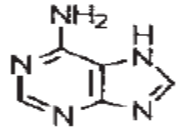
2



Insertion of incorrect building block

Purine antimetabolite





6-Mercaptopurine from Azathioprine — instead of — Adenine

Pyrimidine antimetabolite

5-Fluorouracil — instead of — Uracil

Cytarabine: Cytosine + Arabinose — instead of — Cytosine + Desoxyribos

Folate Antagonists

- **Folates are essential for the synthesis of both purine nucleotides and thymidylate which are required for DNA synthesis and cell division.**

- **Folic acid is a coenzyme used in the one-carbon transfer step in these metabolic pathways.**

- **In order to function as a coenzyme folic acid must be reduced to tetrahydrofolic acid by the enzyme dihydrofolate reductase (DHFR), first to dihydrofolic acid and then to the tetrahydro form.**

Folate Antagonists

- **Methotrexate is a derivative of folic acid which antagonises DHFR with a high affinity.**
- **Methotrexate is widely used clinically, usually administered orally. It is used against acute lymphocytic leukemia.**
- **Main toxicity is myelosuppression**
- **Rescue method: calcium leucovorin (**Folinic acid)

Pyrimidine antagonists

- **The best known example is Fluorouracil, 5FU, incorporated into DNA and RNA, finally inducing cell cycle arrest and apoptosis by inhibiting the cell's ability to synthesize DNA.**
- **It is widely used in colon cancer.**
- **5-FU is effective in palliative management of carcinoma of breast, colon, pancreas, rectum and stomach in patients who can not be cured by surgery or other means.**
- **Its main toxicities are myelosuppression and gut epithelial damage.**

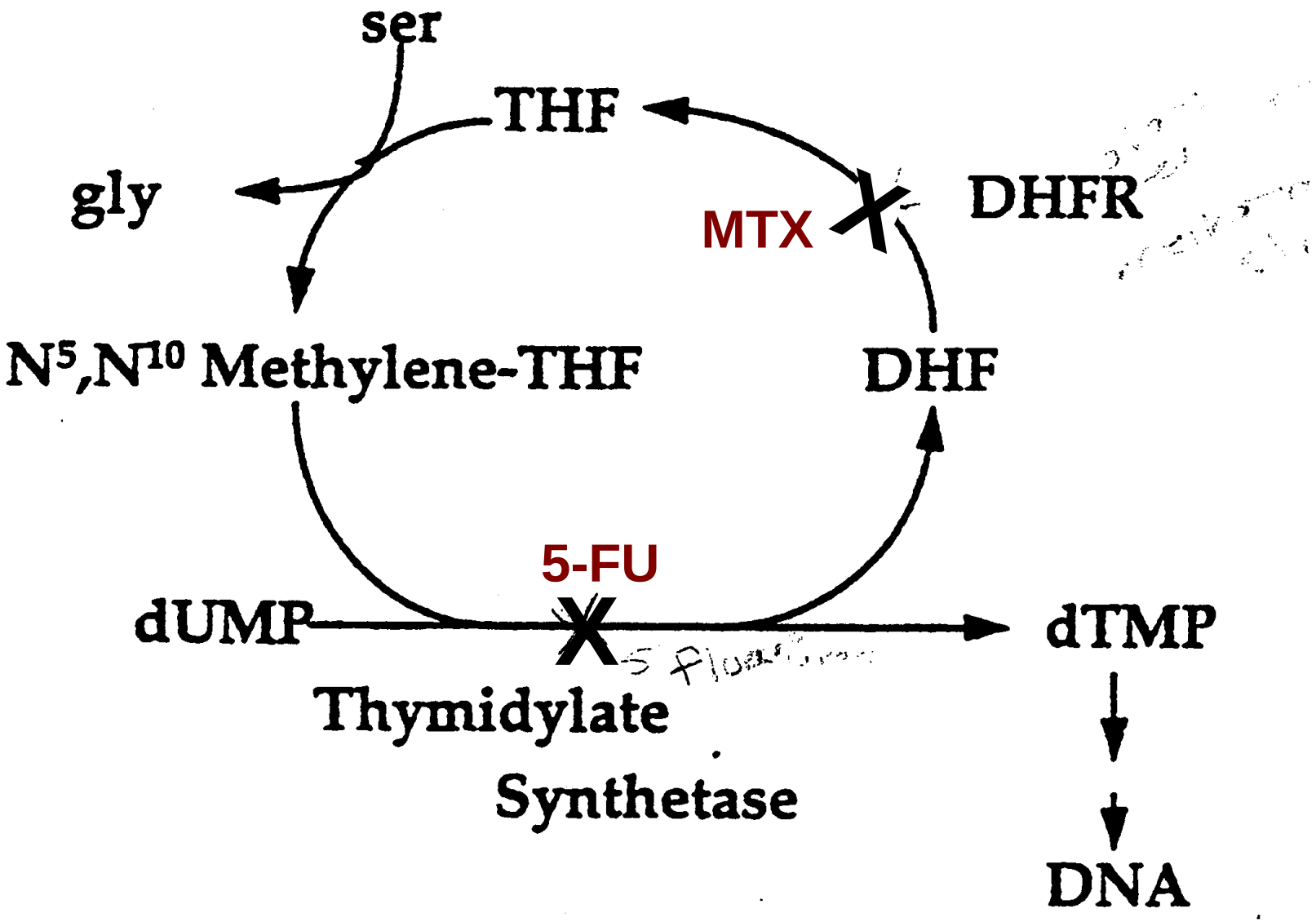
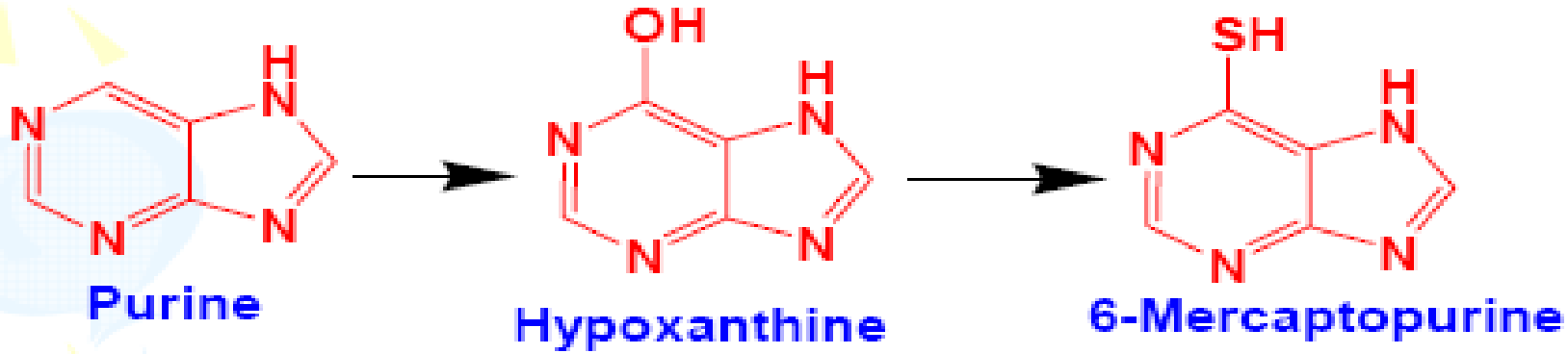


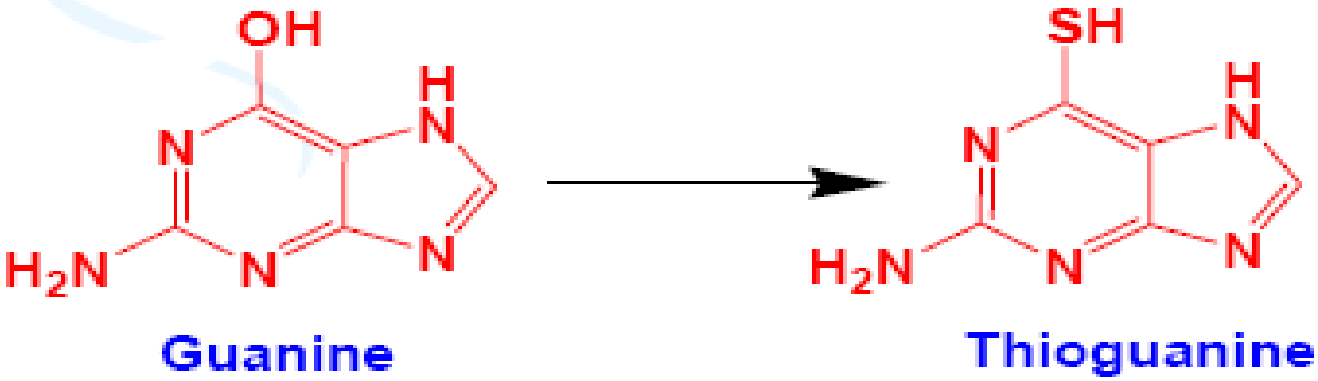
Figure 2. This figure illustrates the effects of MTX and 5-FU on the biochemical pathway for reduced folates.

Purine antagonists

- **1) 6-Mercaptopurine (6-MP)**



2) 6-Thioguanine (6-TG)



Purine antagonist

- **They inhibit various steps in *de novo* purine synthesis and antagonise the enzyme Ribonucleotide Reductase.**
- **Ribonucleotide reductase is a key enzyme in DNA synthesis.**
- **Both 6-MP and 6-TG are administered orally and used for treating acute leukemia.**
- **their main toxicity is to the bone marrow and gut.**
- allpuranoL

MITOTIC SPINDLE INHIBITORS

Inhibition of formation

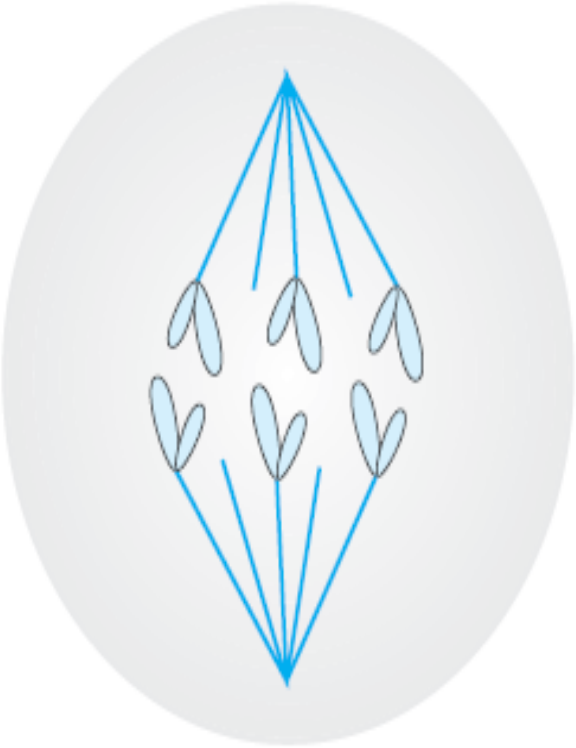
Vinca alkaloids

Microtubules of mitotic spindle

Inhibition of degradation

Paclitaxel

Vinca rosea



Western yew tree

INHIBITORS OF TUBULIN POLYMERISATION

- **The vinca alkaloids Vincristin and Vinblastin are natural products isolated from the periwinkle plant.**

- **They act by binding to tubulin and inhibit its polymerisation into microtubules,**

- **thereby preventing spindle formation during mitosis. This causes dividing cells to arrest at metaphase.**

- **They are widely used in the treatment of solid carcinomas and leukaemias and lymphomas.**

INHIBITORS OF TUBULIN POLYMERISATION

- **Vinblastine therapeutic Uses include Systemic Hodgkin's disease Lymphomas**
- **Vincristine is used against lymphomas, breast cancer, sarcomas, and the various childhood neoplasms.**
- **Vincristine used With prednisone for remission of Acute Leukemia**

Toxicity of the Vinca alkaloids

- **Vinblastine main toxicity is Nausea & Vomiting, Bone Marrow depression, and Alopecia**

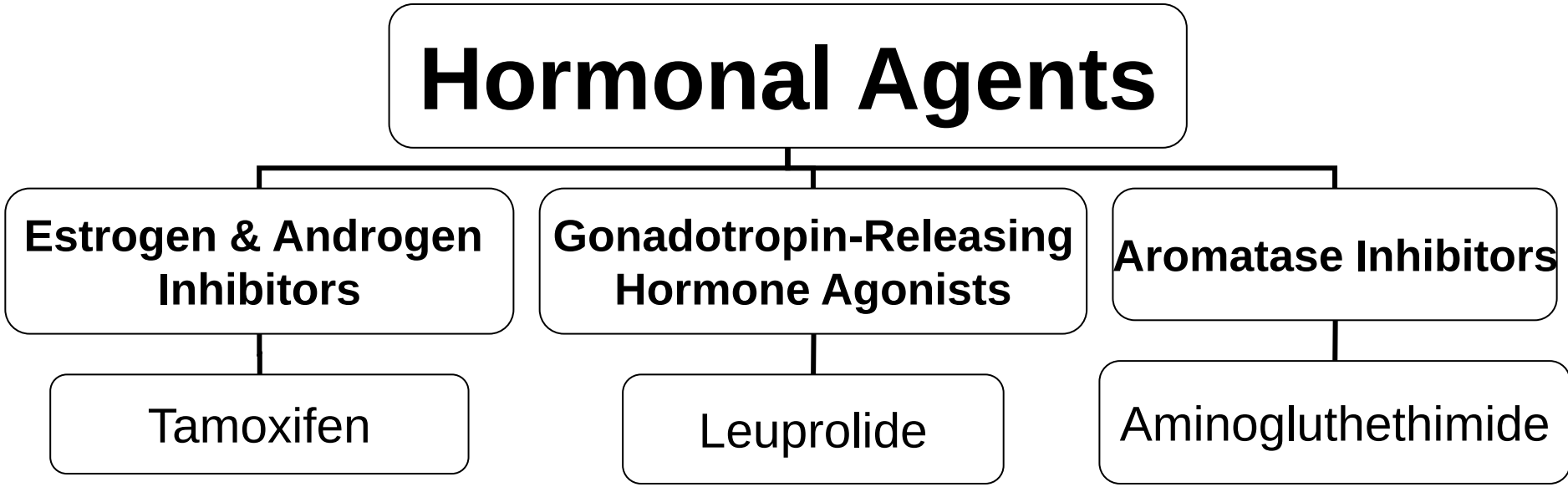
- **While Vincristine is relatively non-toxic, generally having mild myelosuppressive activity but cause they cause sensory changes and neuromuscular abnormalities fairly frequently.**

INHIBITORS OF TUBULIN DE-POLYMERISATION

- **The TAXANES, of which Taxol is the best known example, are isolated from the yew tree.**
- **They also bind to tubulin but have the opposite effect to the Vinca alkaloids and stabilise microtubules to de-polymerisation. (mitotic spindle poison)**

- **The taxanes are generally more toxic than the Vinca alkaloids and side-effects include myelosuppression and Peripheral neuropathy.**

- **Taxol has proven beneficial in late-stage drug-resistant ovarian and breast cancers, prolonging life by about 6 months.**


Hormonal Agents
Estrogen & Androgen Inhibitors
Gonadotropin-Releasing Hormone Agonists
Aromatase Inhibitors
Tamoxifen
Leuprolide
Aminogluthethimide

HORMONE ANTAGONISTS

- **Tumours derived from hormone-sensitive tissues may be hormone-dependent.**

- **Their growth can be inhibited by**

(1) hormones with opposing actions,

(2) hormone antagonists

(3) inhibit hormone synthesis.

Tamoxifen

- Selective estrogen receptor modulator (SERM), have both estrogenic and antiestrogenic effects on various tissues

- Patients with estrogen-receptor (ER) positive tumors are more likely to respond to tamoxifen therapy, while the use of tamoxifen in women with ER negative tumors is still investigational

- When used prophylatically, tamoxifen has been shown to decrease the incidence of breast cancer in women who are at high risk for developing the disease

- **It is active orally and is therefore particularly useful in maintenance therapy.**
- Hot flashes, Fluid retention, nausea.

HORMONE ANTAGONISTS

- **ANTIANDROGENS such as Flutamide bind to androgen receptors and are effective in the treatment of prostate cancer.**

- **Aromatase inhibitors decrease the production of estrogens.**

aminoglutethimide is an example that inhibit hydrocoritoson synthesis.

Anastrozole is the newer agent that have less problem

- The probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m2 of Doxorubicin, 3 to 5% at a dose of 400 mg/m2, 5 to 8% at 450 mg/m2, and 6 to 20% at 500 mg/m2. The risk of developing CHF increases rapidly with increasing total cumulative doses of Doxorubicin in excess of 400 mg/m2.
- jj

Targeted therapy

- **Medication which blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis & tumor growth.**
- **rather than by simply interfering those rapidly dividing cells.**
- **selectively disrupt critical cancer pathways that are deregulated in a given type of cancer.**
- **Targeted therapy can be devided into:**

Small molecules (1)

(2) Monoclonal antibodies

Imatinib

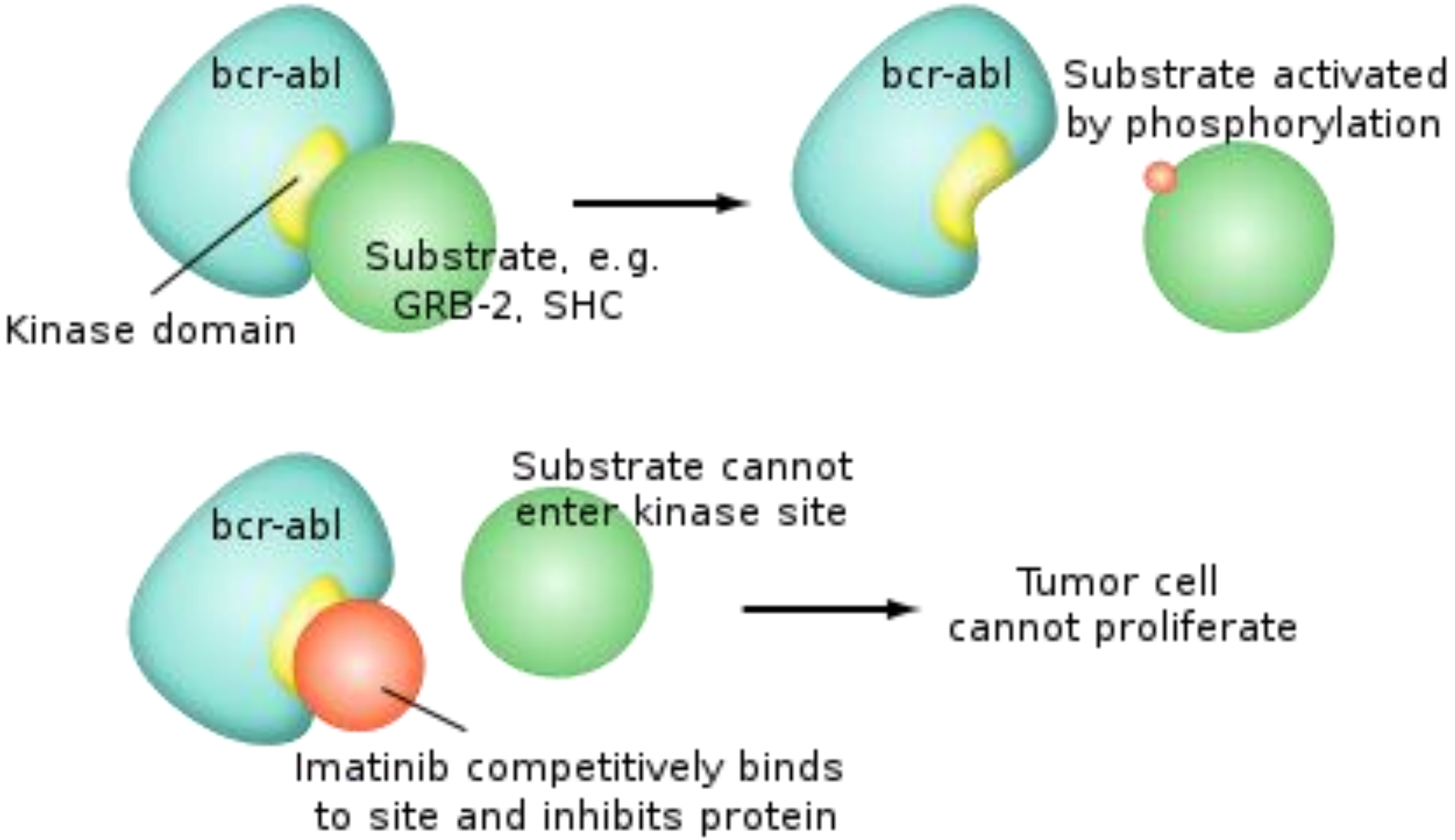
- **Philadelphia chromosome** or **Philadelphia translocation** is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

- **This translocation results in the Bcr-Abl fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease.**

- **Imatinib is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP.**

Imatinib

- It is indicated for the treatment of chronic myelogenous leukemia (CML),
- Imatinib is effective also for treatment of gastrointestinal stromal tumors expressing the c-kit tyrosine kinase
- Side effects– Nausea, muscle pain, fluid swelling, diarrhoea, low white blood counts, liver abnormality

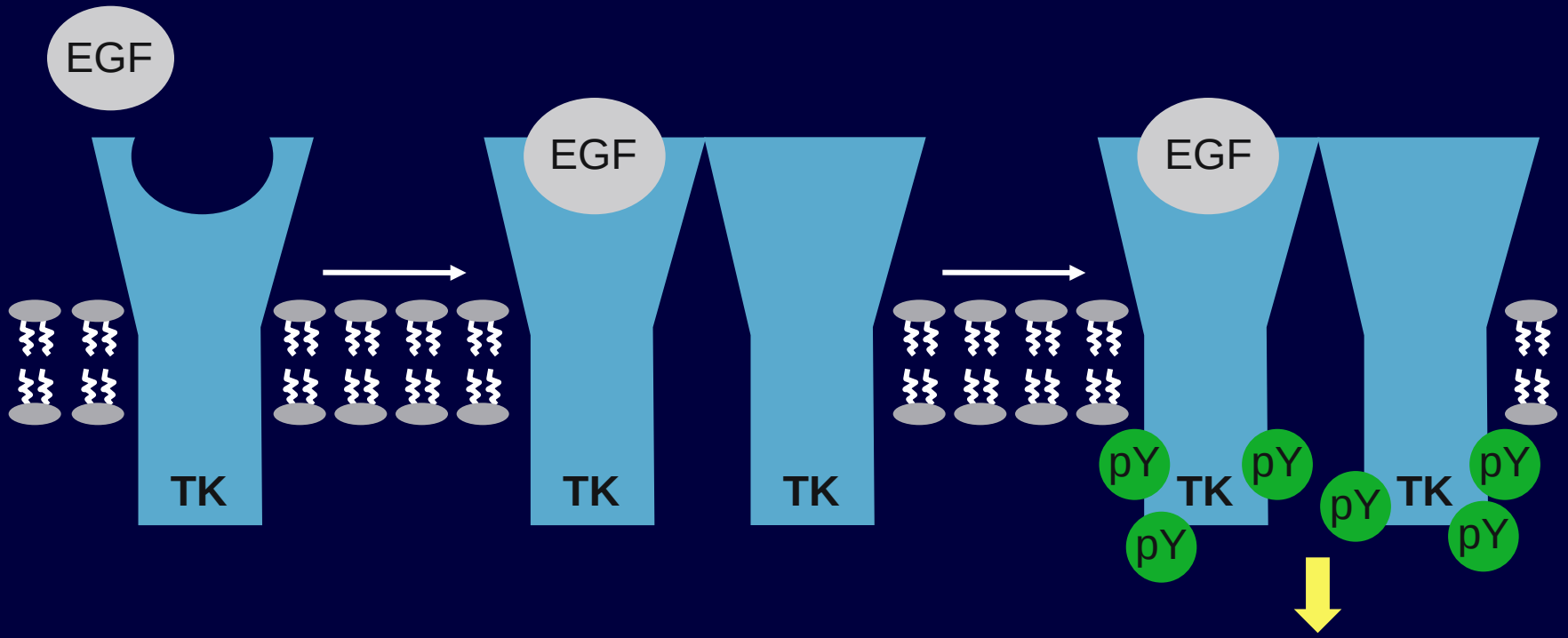


Gleevec is one of the most effective modern medications for cancer treatment,.

Gefitinib

- **is the first selective inhibitor of epidermal growth factor receptor's (EGFR) tyrosine kinase domain.**
- **EGFR is overexpressed in the cells of certain types of human carcinomas - for example in lung and breast cancers.**
- **This leads to inappropriate activation of the anti-apoptotic Ras signal transduction cascade, eventually leading to uncontrolled cell proliferation.**
- **Gefitinib inhibits EGFR tyrosine kinase by binding to the (ATP)-binding site of the enzyme. Thus the function of the EGFR tyrosine kinase in activating the Ras signal transduction cascade is inhibited, and malignant cells are inhibited.**

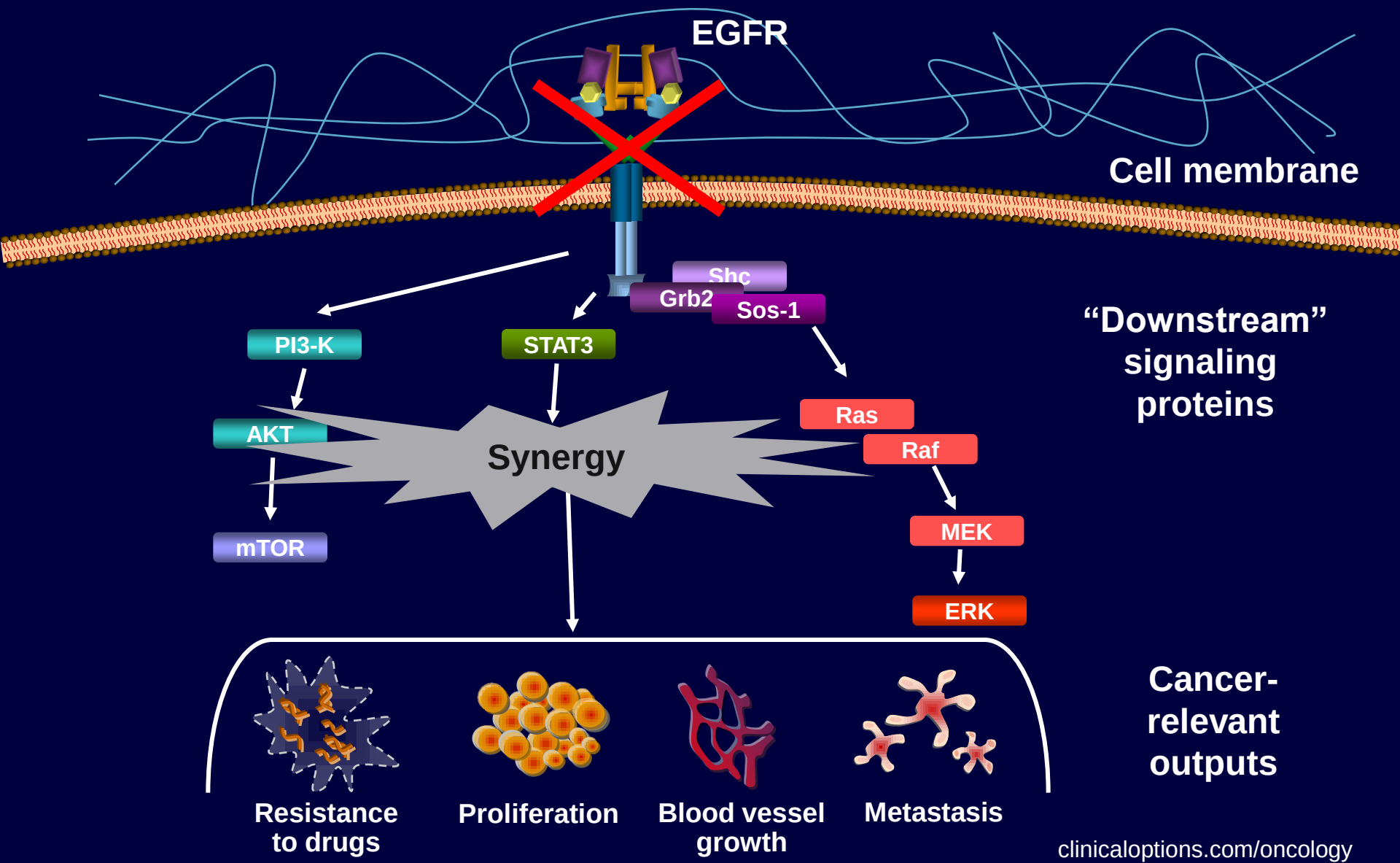
EGF Binds to Receptor Resulting in Dimerization and Autophosphorylation



Activation of intracellular signaling molecules

Increased cell proliferation, inhibition of apoptosis, neoplastic angiogenesis

CLINICAL CARE OPTIONS®
ONCOLOGY



"Downstream" signaling proteins

Cancer-relevant outputs

Types	Name	Trade Name	Target	Indication
Small Molecules	Imatinib (STI-571)	Gleevec	Tyrosine Kinase bcr-abl	CML GIST DFP
	Gefitinib (ZD1839)	Iressa	TK Her1 (ErbB-1)	NSCLC
	Erlotinib	Tarceva	TK	NSCLC
	Bortezomib	Velcade	Proteasome	MM
Monoclonal Antibodies	Rituximab (antiCD20)	**MabThera**	CD20, antibody-dependent cellular cytotoxicity & complement-mediated cytotoxicity	NHL
	Trastuzumab (anti-HER2)	Herceptin	TK Her2(ErbB-2)	CA Breast
	Cetuximab	Erbitux	EGFR, antibody-dependent cellular cytotoxicity	CA Colon H&N Cancer
	Bevacizumab	Avastin	VEGF	CA Colon CA Breast NSCLC

Cetuximab

- An epidermal growth factor receptor (EGFR) inhibitor for treatment of metastatic colorectal cancer and head and neck cancer.
- EGFR overexpression associated with malignant trans formation (60% to 80% of colorectal cancers overexpress EGFR).
- Cetuximab is, preventing ligand binding and activation of the EGFR receptor. This blocks the downstream signaling of EGFR resulting in impaired cell growth and proliferation.
- One of the side effects of Cetuximab therapy is the incidence of, possibly severe, acne-like rash.

Bevacizumab

inhibits the action of VEGF, a blood vessel growth Factor When VEGF is bound to Bevacizumab, it cannot stimulate the formation and growth of new blood vessels

- **prevents VEGF from binding to its receptor**
- **adds to the effects of chemotherapy in cancers like bowel and lung**
- **FDA approved for:**
  - **First-or second-line Colorectal cancer treatment in combination with 5-fluorouracil-based chemotherapy**
  - **Unresectable, locally advanced, recurrent or metastatic nonsquamous non-small-cell lung cancer in combination with carboplatin and paclitaxel**

Bevacizumab

Serious side effects include:

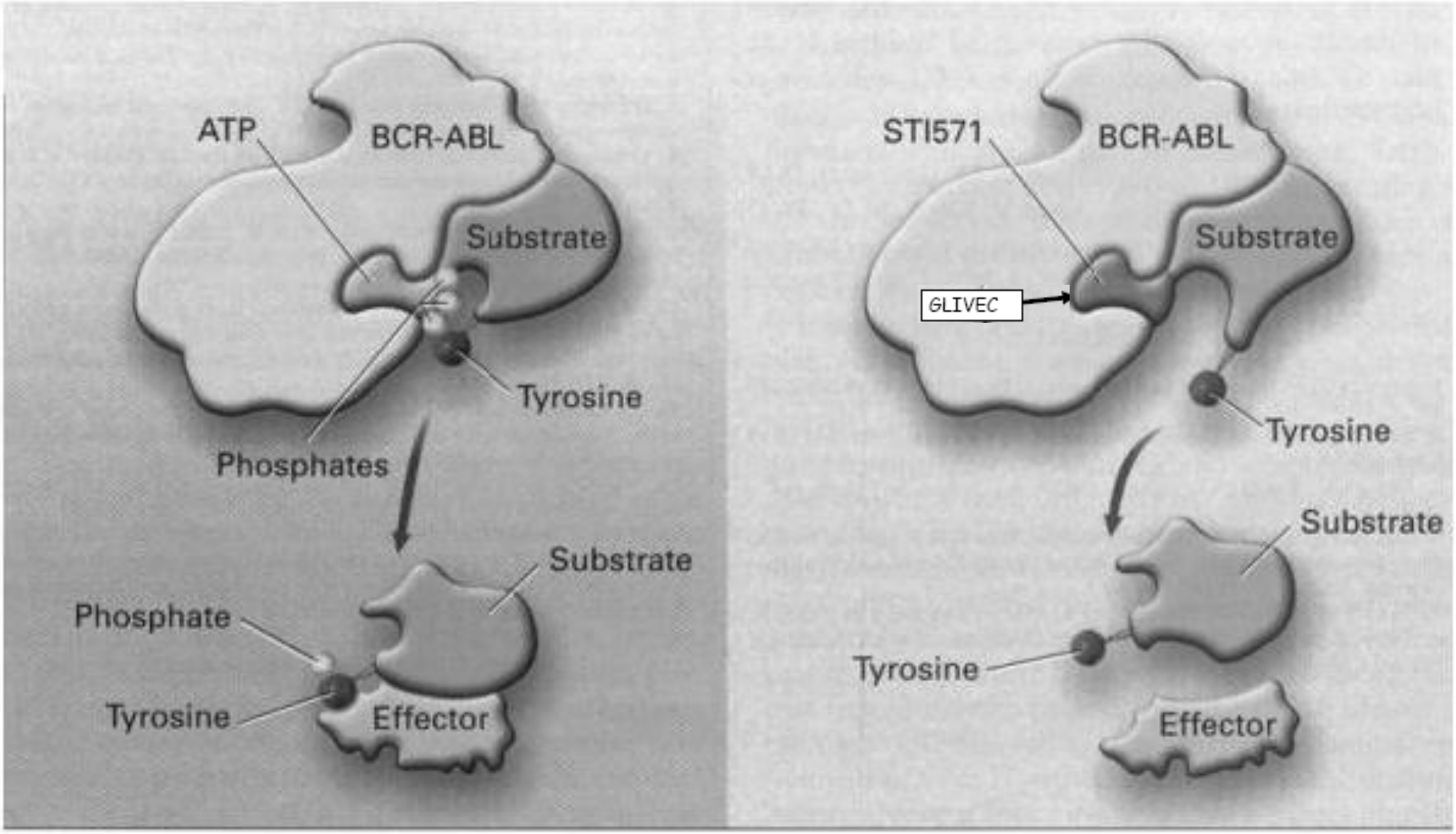
- bowel perforation
- impaired wound healing
- bleeding
- kidney damage

More common side effects of Are:

- high blood pressure
- tiredness/weakness
- clots in veins
- diarrhea

Trastuzumab

- **HER2 (epidermal growth factor receptor family) is overexpressed in 25% to 30% of breast cancers**
- **Trastuzumab is an anti-HER2 monoclonal antibody for HER2-positive metastatic breast cancer treatment**
- **Approved for adjuvant treatment of HER2-positive breast cancer (in combination with doxorubicin, cyclophosphamide, and paclitaxel) in 2006**



Goldman JM, Melo JV. *N Engl J Med*. 344:1084-1086.

Examples

- Until recently, GISTs were notorious for being resistant to chemotherapy, with a success rate of <5%. Recently, the *c-kit* tyrosine kinase inhibitor imatinib (Glivec/Gleevec), a drug initially marketed for chronic myelogenous leukemia, was found to be useful in treating GISTs, leading to a 40-70% response rate in metastatic or inoperable cases.

Reasons for treatment failure

- **Chemotherapy is able to cure only about 10-15 % of all cancer patient.**

- **Either the patient presents**

  (1) with a tumour that is already non-responsive or

  (2) the tumour initially regresses only to return later in a drug-refractory form.

- **The main problem in treatment failure is DRUG RESISTANCE not a lack of selectivity for tumour cells.**

Targeted therapy

- **Medication which blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis & tumor growth.**

- **rather than by simply interfering those rapidly dividing cells.**

- **selectively disrupt critical cancer pathways that are deregulated in a given type of cancer.**

- **Targeted therapy can be divided into:**

(1) Small molecules

(2) Monoclonal antibodies

The origins of resistance lie in the following issues

(1) GENOMIC INSTABILITY AND HYPERMUTABILITY

- **The de-regulated genome →→ genetically heterogeneous tumour**

- **Damage to DNA repair genes is critical →→ → more heterogeneousity as the disease progresses.**

- **From a pharmacological perspective at the biochemical level the tumour is a constantly changing target.**
- **Thus, the primary tumour can be biochemically distinct from metastatic deposits**
- **and one person's colon cancer can be biochemically different from another persons.**

(2) Tumour Cells Are Not Immunogenic

Tumour cells evade immune detection by down-regulating their MHC antigens

So they can't be recognised by antigen-presenting and activated killer T-cells.

(3) The Numbers Game

- **1 x 10^8 tumour cells are visible on an X-ray.**
- **1 x 10^9 cells is a palpable lump weighing a gram.**
- **1 x 10^{12} cells weighs a kilogram and the patient is dead.**
- **Cancer is hard to detect in its early stages and may already have grown to 10^{10} - 10^{11} cells at presentation.**

- **You've got to kill every single cell by drug treatment,**

- **No immunological moping-up of residual tumour!**

- **If there are 10^{11} tumour cells present (100g), killing 99.99% of them leaves 1 x 10^7 residual cells.**
- **1 L1210 leukaemia cell will kill a mouse.**

(4) Poor Tumour Vasculature

- **Tumour masses can only grow to a diameter of about 200 microns before they run into trouble with nutrient supplies.**

  To grow larger they must develop their own vasculature which they do by producing angiogenic growth factors.

- **However, these blood vessels are of a poorer quality than normal which leaves parts of the tumour without nutrients and oxygen.**

Poor Tumour Vasculature

- This generates regions of hypoxia in the tumour mass where cells come out of the growth cycle and sit, alive but non-proliferating, in G_0.

- Unfortunately, hypoxic cells in G_0 are resistant to all anticancer drugs.

- Thus, hypoxic cells become a pharmacological sanctuary from which the tumour can be re-populated after a round of drug treatment when surviving cells may get the opportunity to be re-oxygenated.

(5) Deregulation of apoptosis

THIS IS THE BIG DADDY OF THEM ALL!

The genomic instability of tumour cells inevitably leads to deregulation of the apoptotic pathways.

This results in a generalised reduction in the sensitivity to all forms of cellular insult.

THE REAL BRICK WALL.