# Anti-neoplastic Drugs II

Dr. Yousef Al-saraireh
Assistant Professor
Faculty of Medicine

# Anti-neoplastic Drugs

1. Antimetabolites
2. Antibiotics
3. Alkylating agents
4. Microtubule inhibitors
5. Topoisomerase inhibitors
6. Steroid hormones & their antagonists
7. Monoclonal antibodies
8. Others

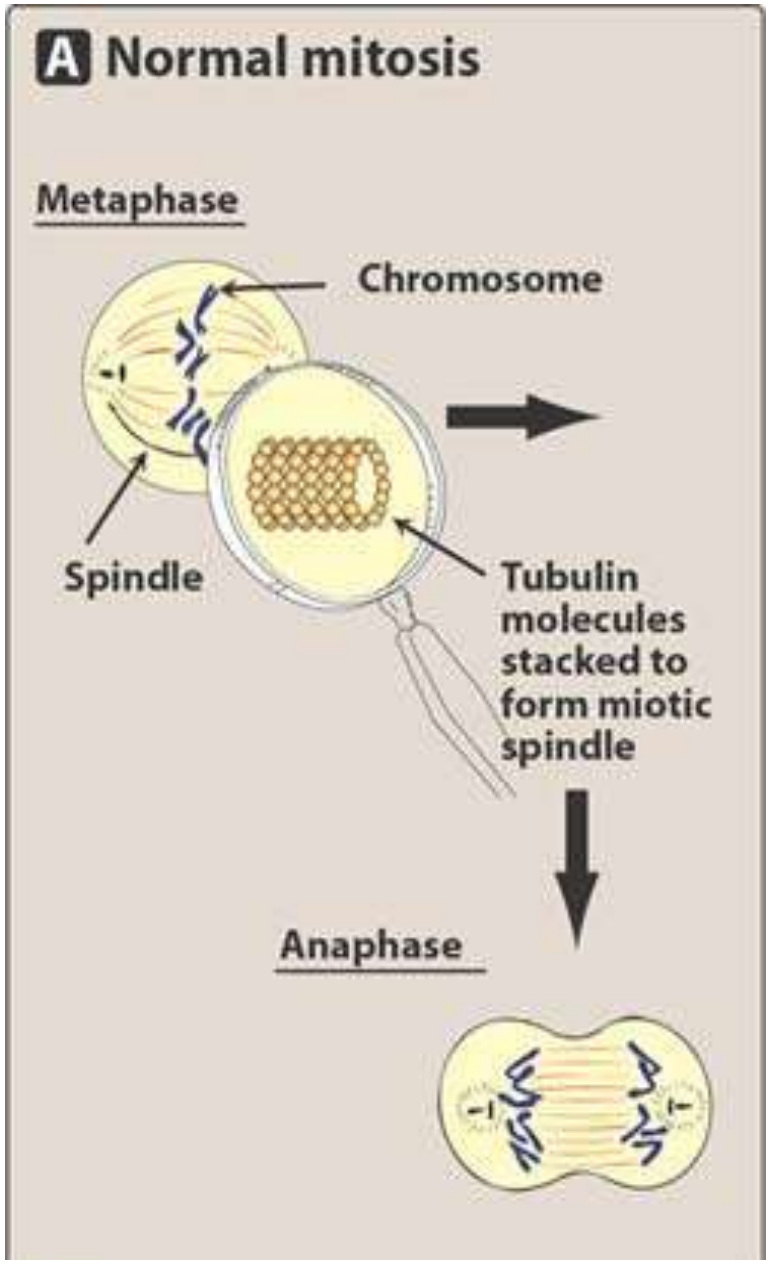
# 4.Microtubule inhibitors

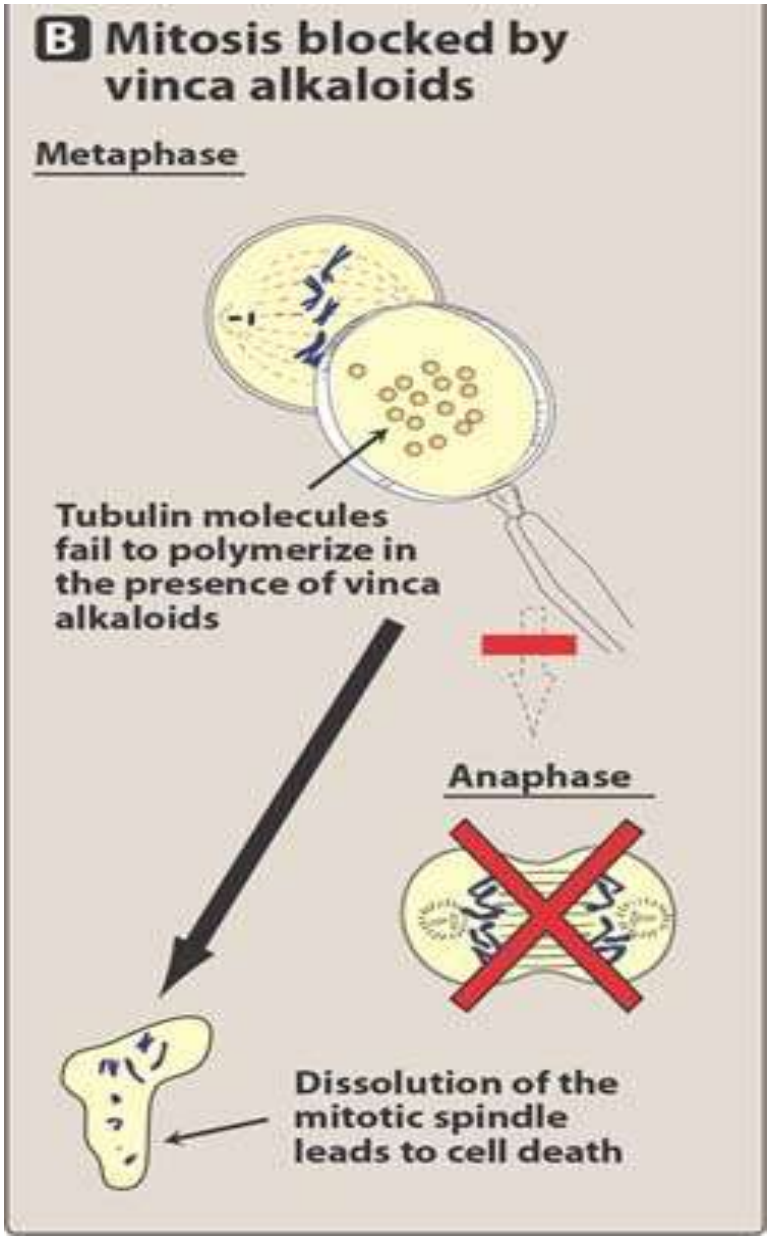
## A. Vinca alkaloids :

- They include mainly Vincristine (Oncovin) and Vinblastin (Velban).
- These are obtained from the Periwinkle plant
- cell-cycle specific & phase specific, because they block mitosis in metaphase (M phase).

Mechanism of action

They bind to tubular protein (Tubulin) to cause its depolymerization , thus prevent assembly of tubulin diamers into micro-tubules which would prevent the formation of mitotic spindle; they act mainly in mitosis phase of cell cycle leading to arrest of mitosis in metaphase stage .


A Normal mitosis
Metaphase
Chromosome
Spindle
Tubulin molecules stacked to form miotic spindle
Anaphase


B Mitosis blocked by vinca alkaloids
Metaphase
Tubulin molecules fail to polymerize in the presence of vinca alkaloids
Anaphase
Dissolution of the mitotic spindle leads to cell death

Uses:

Vincristine is used IV for:

- Acute lymphoblastic leukemia in children
- Wilms' tumor
- Ewing soft-tissue sarcoma
- Hodgkin & non-Hodgkin lymphomas

Vinblastin is used IV for:

- With bleomycin & cisplatin for metastatic testicular carcinoma
- Hodgkin & non-Hodgkin lymphomas

Adverse effects:

- Vincristine is relatively not myelotoxic, but is neurotoxic and thus may cause peripheral neuropathy and also autonomic neuropathy;

- Vinblastine is mainly toxic to bone marrow but least neurotoxic; both may cause local thrombophlebitis and alopecia .

## B. Taxanes :

- **Paclitaxel and Docetaxel**
- These plant alkaloids are obtained from Western or European yaws (Taxus).
- They are cell-cycle specific

Mechanism of action

- In comparison to Vinca alkaloids, these drugs enhance polymerization of tubulin and this would prevent microtubule dis-assembly into tubulin monomers, thus preventing separation of chromosomes and also causing arrest of mitosis in metaphase stage .

Uses

They are useful IV for wide variety of cancers such as advanced breast or ovarian cancer;

Adverse effects

They may cause myelosuppression, peripheral neuropathy and , with paclitaxel , anaphylactic reaction (due to vehicle)

# 5. Topoisomerase (Top) inhibitors

- Tops are essential enzymes involved in maintaining DNA structure during replication and transcription
- They cleave DNA strands and form intermediates with the strands, producing a gap through which DNA strands can pass, then reseal the strand breaks.
- Top I produces single-strand breaks; Top II produces double-strand breaks.

<u>Mechanism of action</u>

- These drugs bind Topisomerases to inhibit its function, and thus cause DNA strand breaks.
- They are cell cycle specific

1. **Epipodophylotoxins :**

- Etoposide and teniposide
- This is semisynthetic and is derived from podophylotoxin that is obtained from the mayapple (mandrake) root.
- They inhibits Top II.
- They are given orally and sometimes IV for small cell lung cancer, lymphoma, testicular cancer, and acute monocytic leukemia.
- They cause bone marrow toxicity, stomatitis and vomiting .

**2. Camptothecin :**

- Obtained from a Chinese tree.
- Irinotecan and topotecan
- They inhibits Top I.

Uses:

A. Irinotecan

Colon cancer; NSCLC; SCLC; cervical and ovarian cancers; gastric cancer and pancreatic cancer

B. Topotecan

Ovarian cancer and SCLC

Adverse effects

diarrhea and bone marrow depression

# 6. Steroid hormones & their antagonists

- Tumors that are steroid hormone-sensitive may be either:

- Hormone-responsive tumor: tumor regresses following treatment with hormone
- Hormone-dependent tumor: removal of hormonal stimulus causes tumor regression

- e.g. Antiestrogen (Tamoxifen) in breast cancer

## A. Prednisone

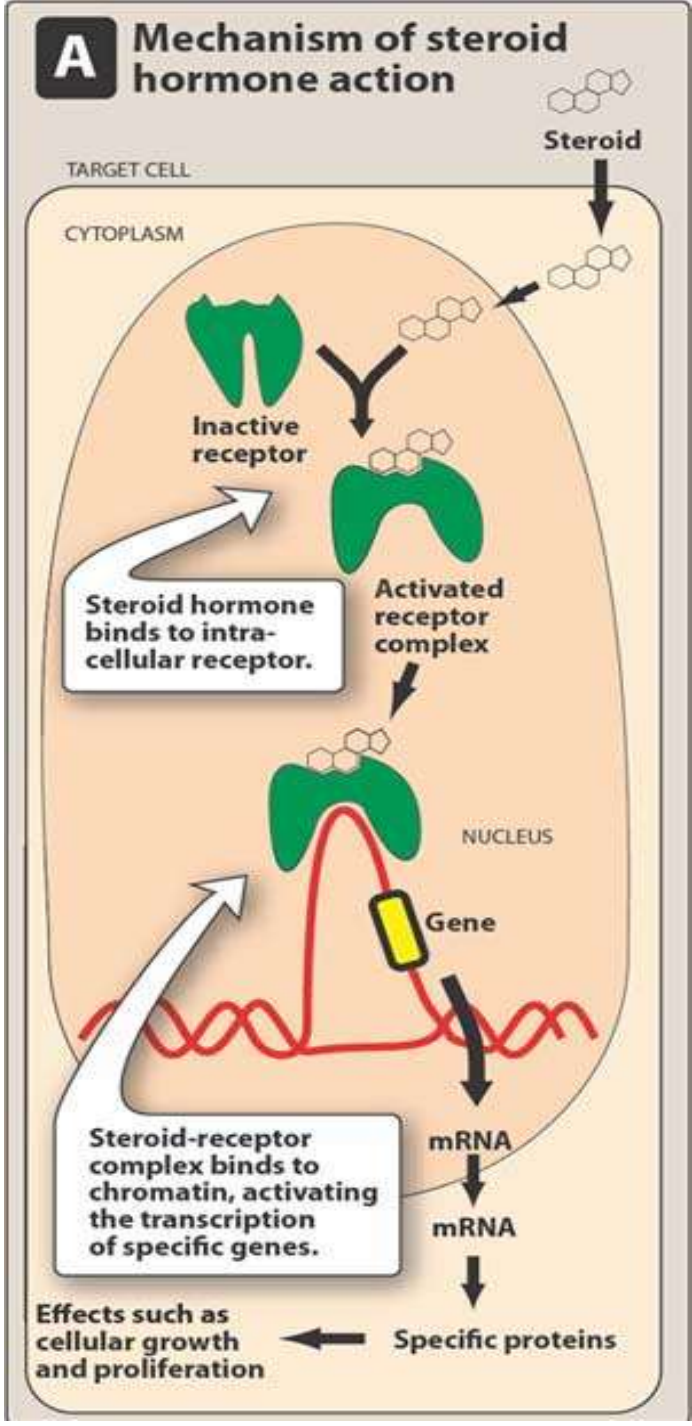
- Is a potent anti-inflammatory corticosteroid
- Is used to induce remission in patients with acute lymphocytic leukemia and, Hodgkin & non-Hodgkin lymphomas

Mechanism of action

- Prednisone is inactive, must be reduced to prednisolone, binds to intracellular receptor that triggers production of specific proteins
- Is given orally

Adverse effects:

- Predisposition to infections, ulcers & pancreatitis, hyperglycemia, cataract, glycauma, osteoporosis & change in mood



## B. Tamoxifen

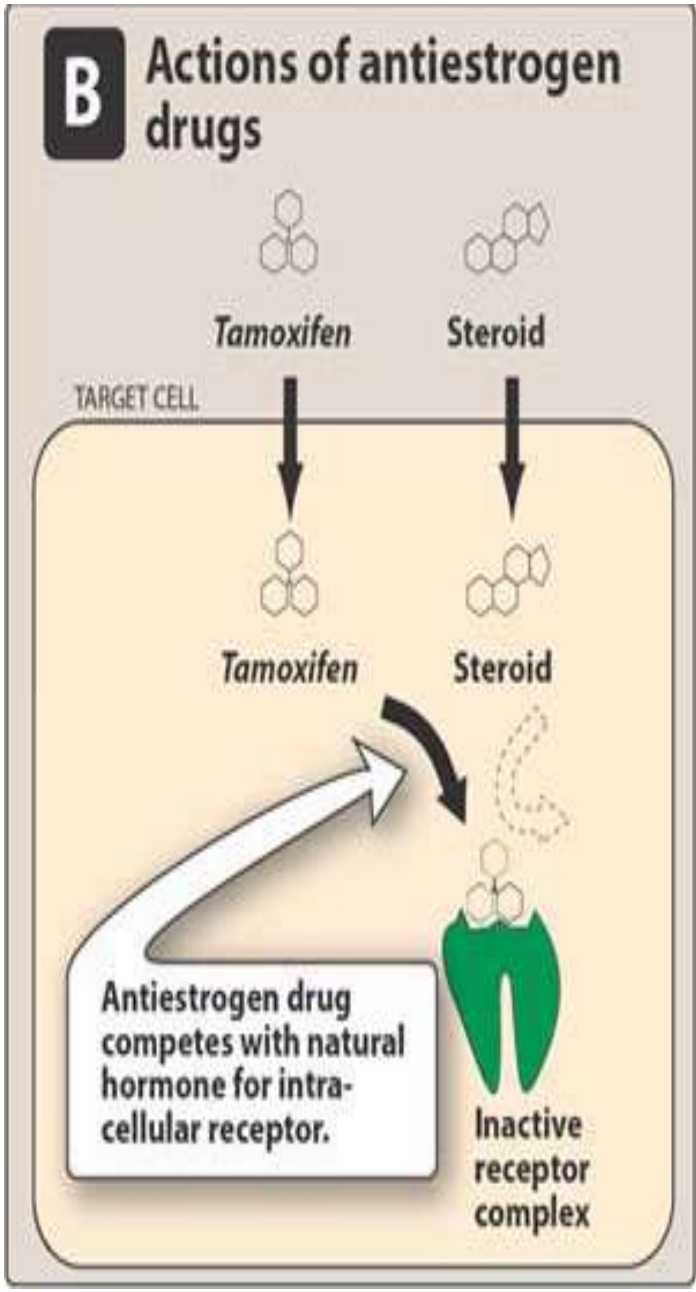
- Is an estrogen antagonist
- Is a selective estrogen-receptor modulator (SERM)
- Has weak estrogenic activity

<u>Mechanism of action</u>

- Tamoxifen binds to estrogen receptor forming inactive drug-receptor complex, resulting in inhibition of tumor growth

<u>Uses</u>

- First-line therapy in treatment of estrogen-receptor-positive breast cancer



- Is given orally

Adverse effects:

- Hot flashes, nausea, vomiting, skin rash, vaginal bleeding & discharge, hypercalcemia, endometrial cancer, thromboembolism

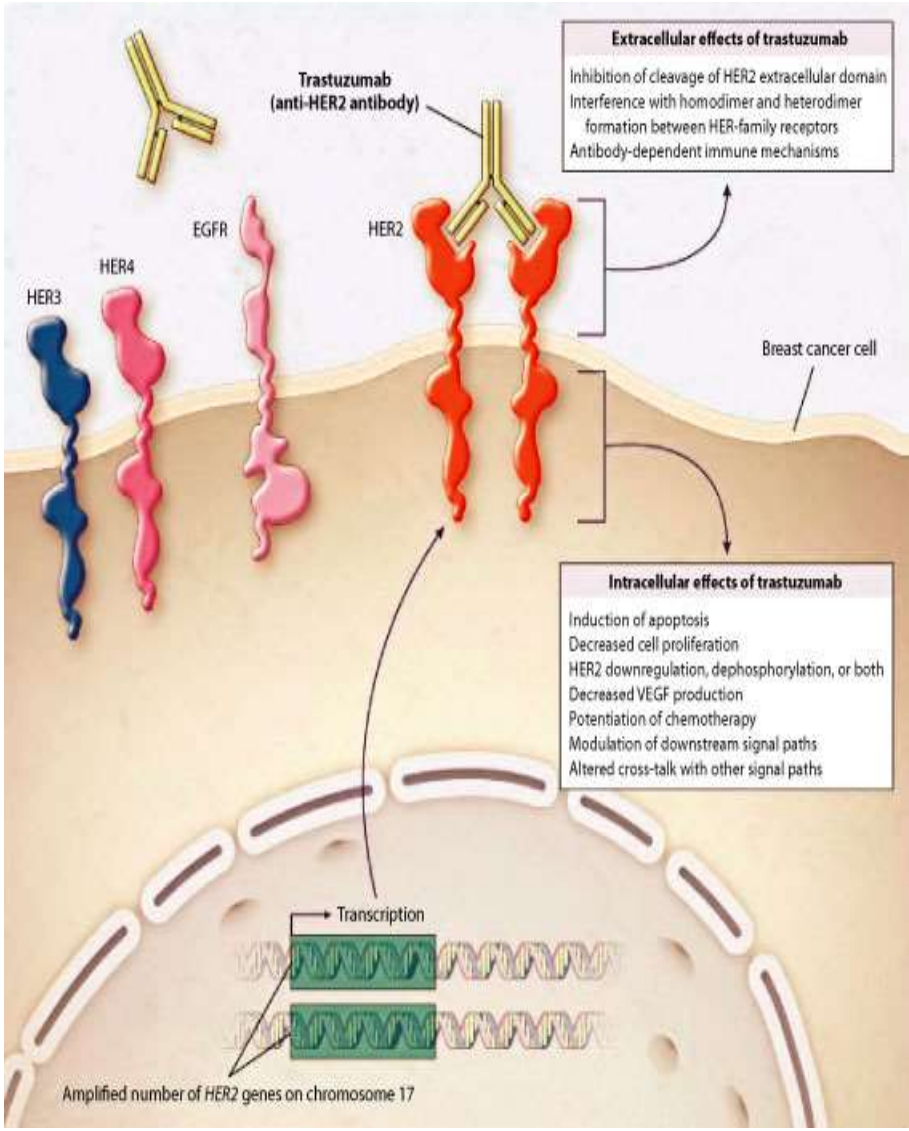
# 7. Monoclonal antibodies

- They are directed against specific tumour-associated antigens
- Have fewer side effects

## A. Trastuzumab

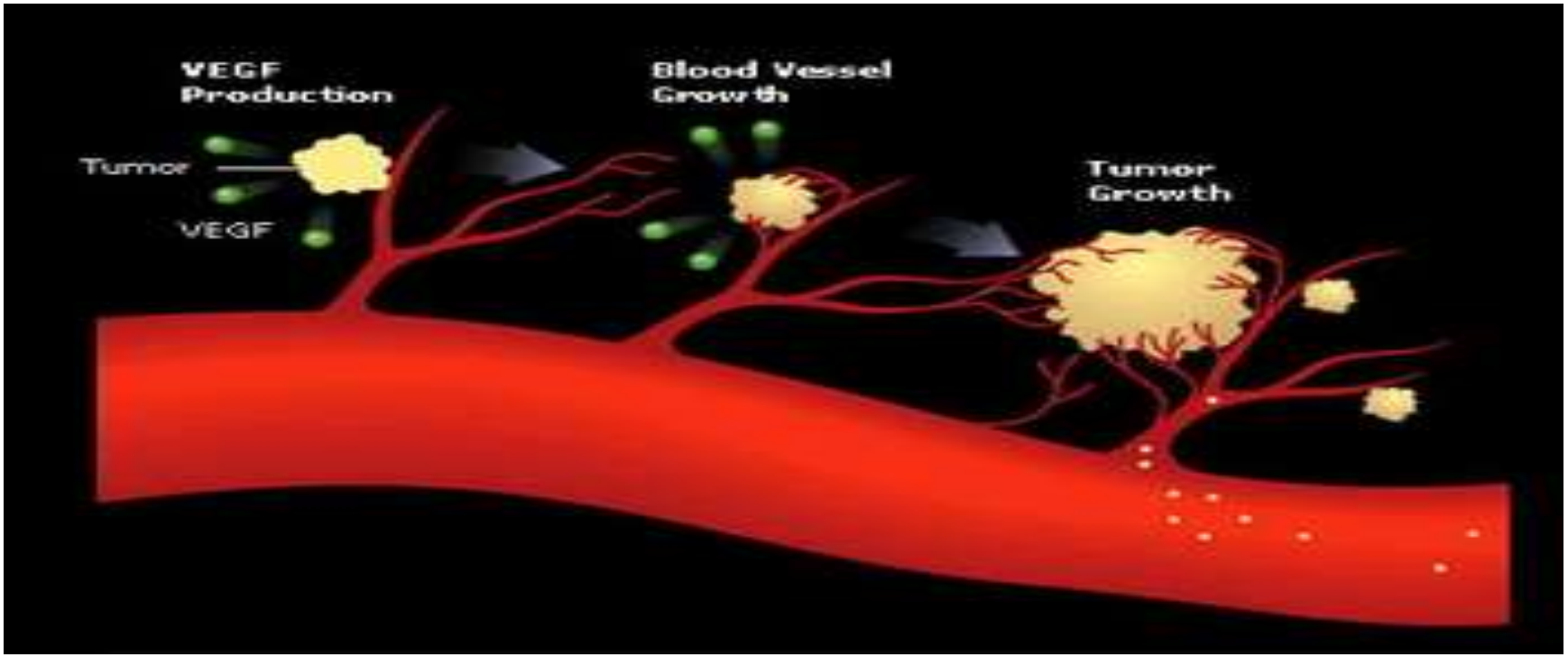
- It binds to extracellular domain of the human epidermal growth factor receptor HER-2/*neu.*
- It blocks the natural ligand from binding and down-regulates the receptor.
- It is approved IV for the treatment of metastatic breast cancer in patients whose tumors overexpress HER-2/*neu*

- Adverse effects include congestive heart failure, fever, chills



## B. Bevacizumab

- first in a new class of anticancer drugs called antiangiogenesis agents.
- It attaches to and stops vascular endothelial growth factor(VEGF) from stimulating the formation of new blood vessels leading to tumor shrinkage and death
- It is approved IV for use as a first-line drug against metastatic colorectal cancer.
- Common adverse effects are hypertension, stomatitis, and diarrhea.



## C. Rituximab

- It binds to the CD20 molecule on malignant B lymphocytes
- is approved for the therapy of patients with non-Hodgkin's lymphoma.

- The mechanism of action includes complement-mediated lysis, antibody-dependent cellular cytotoxicity, and induction of apoptosis in the malignant lymphoma cells.

- Adverse effects include Hypotension, bronchospasm, angioedema, chills and fever.

# 8. Others

## A. Platinum coordination complexes

- Cisplatin, carboplatin, and oxaliplatin: platinum derivatives
- They act similarly to alkylating agents.
- Platinum binds to DNA and forms cross-links between neighboring guanines causing a major bending of the DNA leading to cellular damage.

Uses: IV

non-small cell and small cell lung cancer, esophageal and gastric cancer, head and neck cancer, and genitourinary cancers, particularly testicular, ovarian, and bladder cancer

Adverse effects:

vomiting, nephrotoxicity, ototoxicity, neurotoxicity

# B. Tyrosine kinase inhibitors

## 1. Imatinib:

- It acts as a signal transduction inhibitor, used specifically to **inhibit *bcr-abl* tyrosine kinase**
- It **prevents the phosphorylation of tyrosine** on the substrate molecule and, hence, **inhibits subsequent steps that lead to cell proliferation**
- It is used orally for of **chronic myelogenous leukemia**
- **<u>Adverse effects</u>**

fluid retention and edema, hepatotoxicity, and neutropenia as well as nausea and vomiting

## 2. Gefitinib

- It targets the **epidermal growth factor receptor**.
- It is approved for the treatment of non–small cell lung cancer
- It is administered orally
- The most common adverse effects are **diarrhoea, nausea, and acne-like skin rashes**