ANTICANCER DRUGS

Cancer

- Leading cause of death
- Among women Breast, Lung, colorectal and uterine are the most common
- Among men Prostate, Lung, colorectal and urinary bladder cancer are the most common

- Behavioral and dietary risks:
  - High body mass index
  - Low fruit and vegetable intake
  - Lack of physical activity
  - Tobacco use
  - Alcohol use

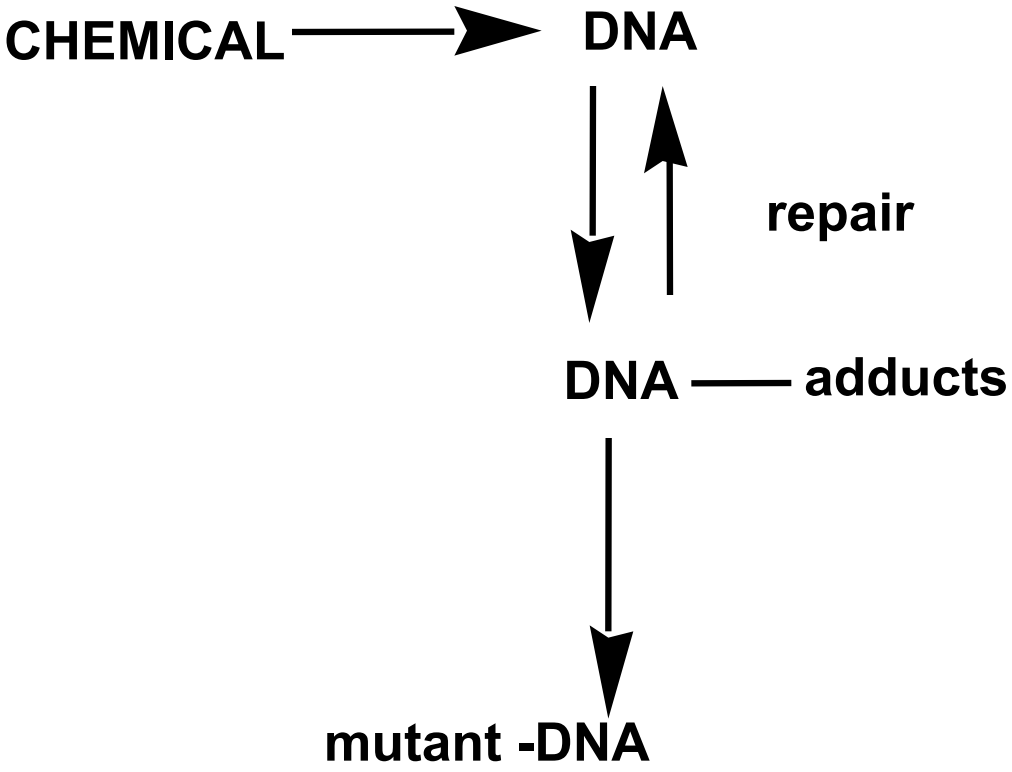
Causes of cancer

- Cancer is basically a disease of cells characterized by a shift in the control mechanisms that govern cell proliferation and differentiation

Causes of Cancer

- Chemical carcinogens (particularly those in tobacco smoke) as well as asbestos, cyclophosphamide, and benzene
- Certain herpes and papilloma group DNA viruses and type C RNA viruses
- Human retrovirus (HTLV-I): Human T cell leukemia
- Damaged tumor suppressor genes
- Various types of radiation
  - UV radiation

Neoplastic Conversion



Carcinogens

Properties of chemical carcinogens:

1. Carcinogenesis is dose dependent
2. Long lag period between exposure and appearance of tumors (in humans $\geq$ 20 years)
3. Carcinogens are subject to activation and degradation
4. Active carcinogens are electrophiles

Example: Benzene, Conjugated Estrogens, Cyclophosphamide

- Cancer cells characteristics :
  - Uncontrolled proliferation
  - Dedifferentiation and loss of function
  - Invasiveness
  - Metastasis
  - Immortality

Oncogenes

Genes that encode for transforming proteins that can cause cancer.

Oncogenes are derived from the mutation of Proto-oncogenes

Proto-oncogenes: genes in normal cells that encode for proteins involved in cellular regulations, including: G proteins, tyrosine-specific kinases, other protein kinases, growth factors and transcription regulators

Tumor suppressor genes: anti-oncogenes

- These are also referred to as growth suppressor genes, in normal cells these proteins suppress cell growth and division mutation leads to a loss of the ability to control cell growth and division the anti-oncogene product is a mutant protein that is inactive as a growth suppressor

- The ultimate goal of chemotherapy is to eradicate neoplastic cells (cure)

- If cure is not possible, the goal is to stop the cancer from enlarging and spreading (controlling the disease)

- Treatment:
  - Surgery
  - Radiation
  - Drug therapy

- Surgery is the most common treatment for solid cancer
- Drug therapy is the most common for disseminated cancers (leukemias, disseminated lymphomas and metastases)
- Drug therapy also plays a major role as adjunct to surgery and irradiation: by killing malignant cells that surgery and irradiation leave behind
  - This reduces recurrence and improves survival

Cancer chemotherapy

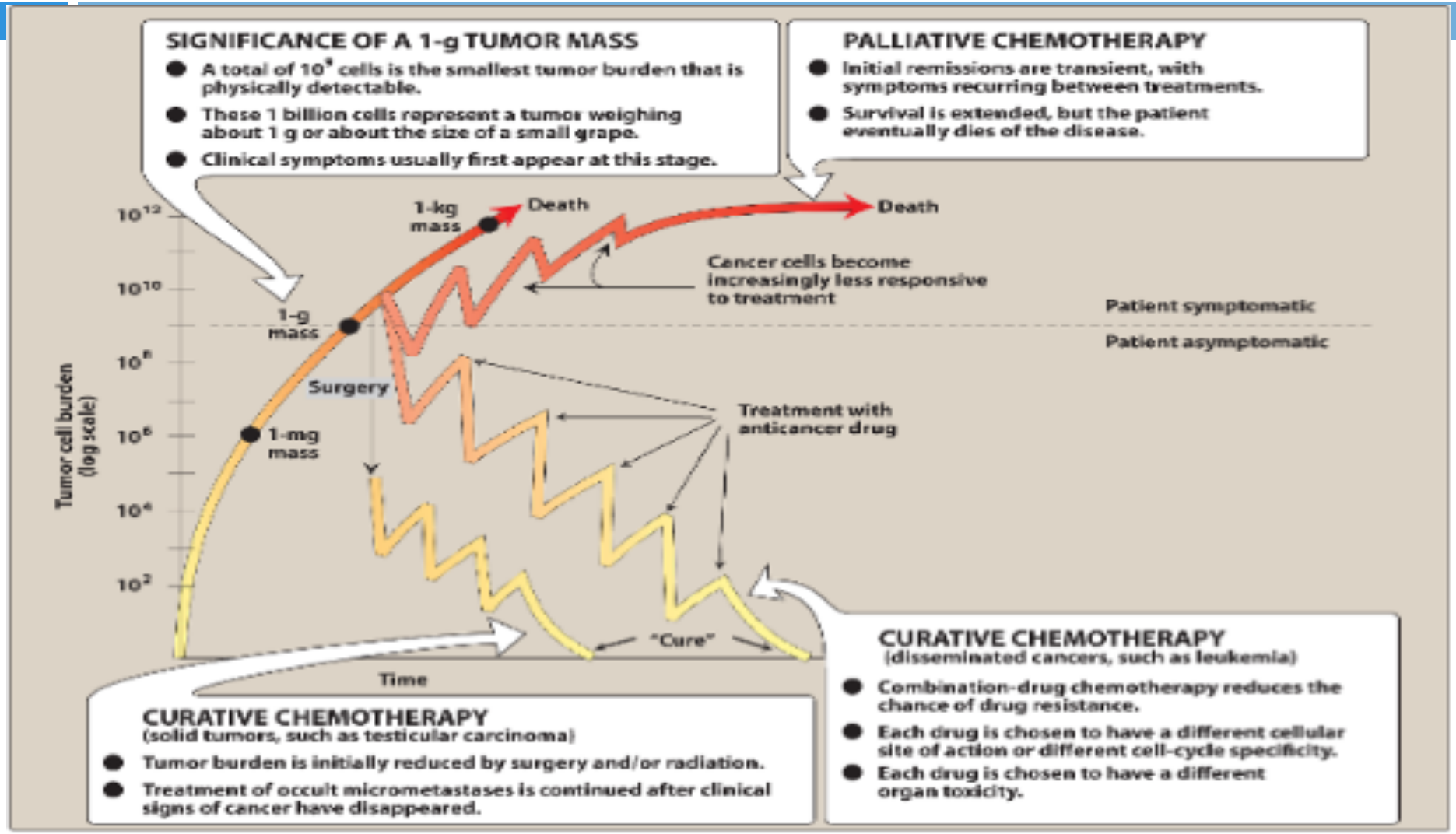
- Aims for lethal cytotoxic effects or promoting apoptosis in cancer cells
- Target DNA or metabolic sites in cell replication
- Ideally should only interfere with cellular processes unique to malignant cells
- Most available anticancer drugs affect both normal and abnormal cells causing therapeutic and toxic effects

TABLE 101.3 ▪ Some Cancers for Which Drugs May Be Curative[a]

Type of Cancer	Drug Therapy[b]
Hodgkin's lymphoma	Doxorubicin + bleomycin + vinblastine + dacarbazine
Burkitt's lymphoma	Cyclophosphamide + vincristine + methotrexate + doxorubicin + prednisone
Choriocarcinoma	Methotrexate ± leucovorin
Small cell cancer of lung	Etoposide + either cisplatin or carboplatin
Testicular cancer	Cisplatin + etoposide ± bleomycin
Wilms' tumor[c]	Dactinomycin + vincristine ± doxorubicin ± cyclophosphamide
Ewing's sarcoma[c]	Cyclophosphamide + doxorubicin + vincristine alternating with etoposide + ifosfamide (with mesna)
Acute myeloid leukemia	Daunorubicin + cytarabine + etoposide
Breast cancer[c]	Fluorouracil + doxorubicin + cyclophosphamide
Colorectal cancer[c]	Fluorouracil + leucovorin + oxaliplatin
Acute lymphocytic leukemia	Vincristine + prednisone + asparaginase + daunorubicin or doxorubicin ± cyclophosphamide

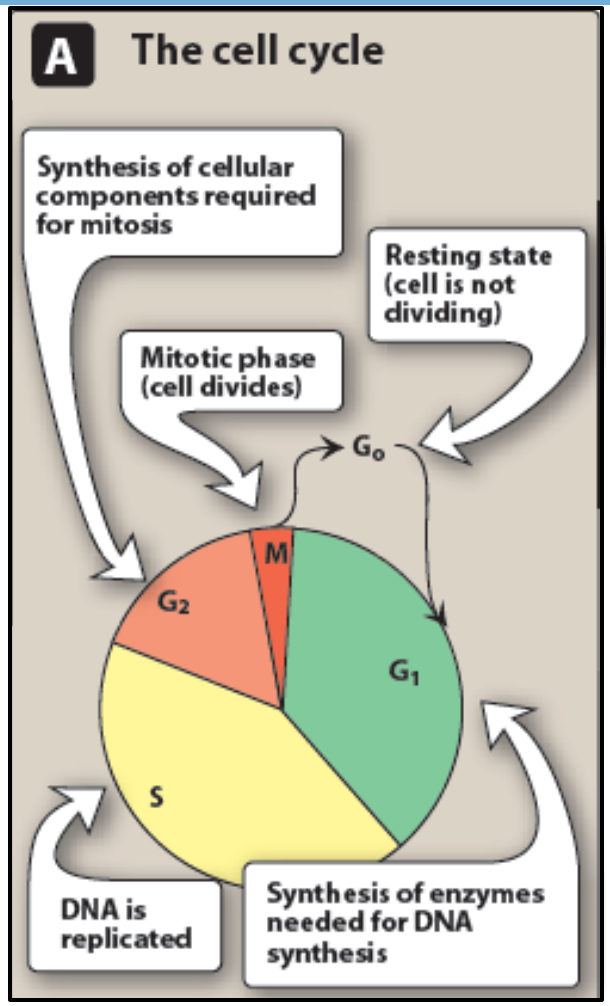
[a]"Cure" is defined as a 5-year disease-free interval following treatme
[b]These are representative regimens. Other regimens may also be high effective.
[c]Chemotherapy is combined with surgery and/or radiotherapy in these

- Anticancer drugs
  - Cytotoxic agents (kill the cells directly)
    - Most commonly used
    - Cancer chemotherapy
  - Hormones and hormone antagonists
  - Biologic agents (immunomodulators)
  - Targeted drugs (bind to specific molecules that promote cancer growth)


SIGNIFICANCE OF A 1-g TUMOR MASS
A total of 10^9 cells is the smallest tumor burden that is physically detectable.
These 1 billion cells represent a tumor weighing about 1 g or about the size of a small grape.
Clinical symptoms usually first appear at this stage.
PALLIATIVE CHEMOTHERAPY
Initial remissions are transient, with symptoms recurring between treatments.
Survival is extended, but the patient eventually dies of the disease.
Tumor cell burden (log scale)
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
1-kg mass
Death
Death
Cancer cells become increasingly less responsive to treatment
1-g mass
Patient symptomatic
Patient asymptomatic
Surgery
Treatment with anticancer drug
1-mg mass
"Cure"
Time
CURATIVE CHEMOTHERAPY
(solid tumors, such as testicular carcinoma)
Tumor burden is initially reduced by surgery and/or radiation.
Treatment of occult micrometastases is continued after clinical signs of cancer have disappeared.
CURATIVE CHEMOTHERAPY
(disseminated cancers, such as leukemia)
Combination-drug chemotherapy reduces the chance of drug resistance.
Each drug is chosen to have a different cellular site of action or different cell-cycle specificity.
Each drug is chosen to have a different organ toxicity.

Cell cycle specificity of drugs

- Rapidly dividing cells are more sensitive to chemotherapy than slowly dividing cells
- Non-proliferating cells usually survive the toxic effects of many of these agents



Tumor growth rate

- Tumor growth rate is rapid initially but decreases as the tumor size increases

- Reducing tumor burden through surgery or radiation promotes the active proliferation of the remaining cells and increases their susceptibility to chemotherapy

Combination chemotherapy

- Cytotoxic agents with different toxicities, molecular sites and mechanisms of action are given in combination at full dose

- Treatment protocols; for certain neoplastic states
  - Example: **POMP** for acute lymphocytic leukemia
    - **P**rednisone
    - **O**ncovin® (vincristine)
    - **M**ethotrexate
    - **P**urinethol ® (mercaptopurine)

Combination chemotherapy

- Advantages:

  1. Provide maximal cell killing within tolerated toxicity

  2. Affect a broader range of cell lines

  3. May delay or prevent the development of resistant cell lines

  4. Reduce injury to normal cells

Combination chemotherapy

- Guidelines for drug selection
  - Each drug should be effective
  - Each drug should have a different mechanism of action
  - Minimal overlapping toxicities

- Therapy is scheduled intermittently (21 days apart)
  - To allow recovery of the patient's immune system which is also affected
  - To reduce the risk of serious infections

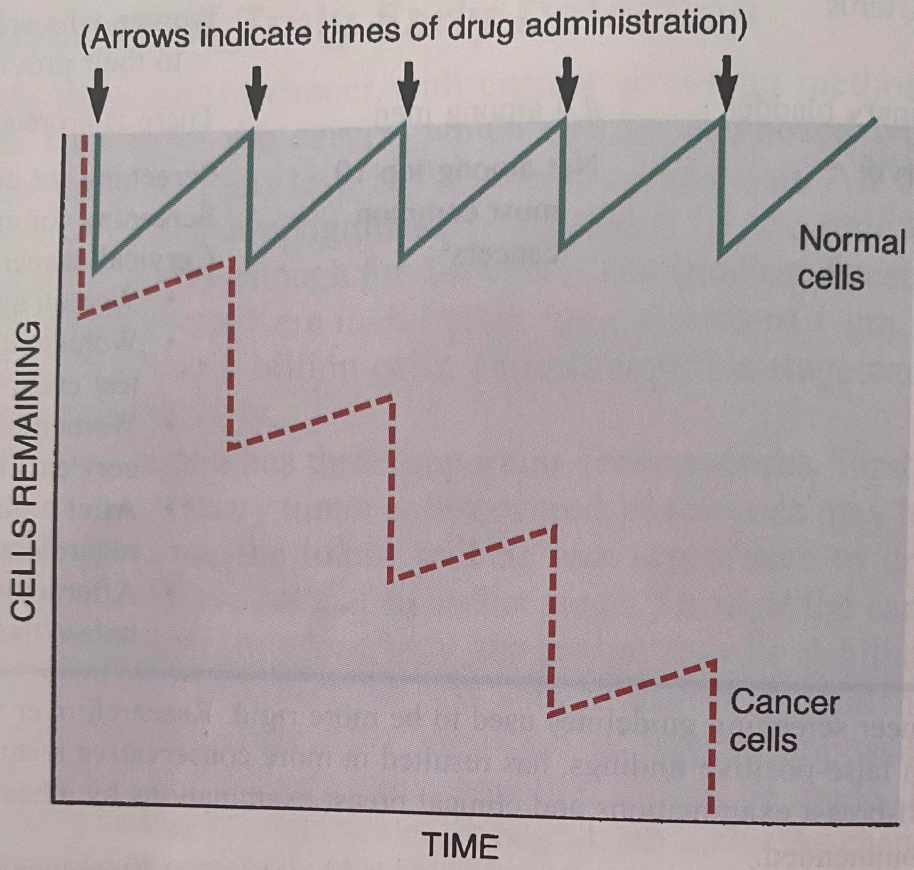


Fig. 101.3 ■ Recovery of critical normal cells during intermittent chemotherapy.

Cancer cells and normal cells (e.g., cells of the bone marrow) are killed each time cytotoxic drugs are given. In the interval between doses, both types of cells proliferate. Because, in this example, normal cells repopulate faster than the cancer cells, normal cells are able to recover entirely between doses, whereas regrowth of the cancer cells is only partial. As a result, with each succeeding round of treatment, the total number of cancer cells becomes smaller, whereas the number of normal cells remains within a tolerable

Problems with Chemotherapy

- Problems with Chemotherapy
  - Resistance
  - Toxicity to normal cells (Can be dose limiting; immunosuppression)
    - Especially to cells with high growth fraction

    (bone marrow, GI epithelium, hair follicles, sperm forming cells)
  - Treatment induced tumors
    - Because a lot of antineoplastic drugs are mutagens

Major toxicities of chemotherapeutic drugs

- Bone marrow suppression
  - Neutropenia. Thrombocytopenia, Anemia
- GI injury
  - Stomatitis, Diarrhea
- Nausea and vomiting
- Alopecia
- Reproductive toxicity
- Local injury
- Other unique toxicities: Nephrotoxicity
- Carcinogenesis

Chemotherapy mechanisms

- Cancer drugs inhibit cell proliferation
- Tumor cells are rapidly proliferating and thus especially sensitive
- Other rapidly proliferating tissues (bone marrow, hair, GI and oral mucosa) are adversely affected
- Nausea and vomiting is common
- Prochlorperazine and ondansetron can be used to prevent nausea

Chemotherapy mechanisms

- Resistance can occur with all anticancer drugs
- P-glycoprotein in cell membranes pumps out toxins and may be responsible for resistance of cells to many anticancer drugs
- Useful to employ multiple agents if they act on different parts of the cell cycle
- Use different agents with different toxicities

Cytotoxic anticancer drugs

- Alkylating agents
- Antimetabolites
- Antitumor antibiotics
- Microtubule inhibitors

Alkylating agents

- Bind covalently to nucleophilic groups on cell constituents
- DNA alkylation is lethal to tumor cells
- Most toxic for rapidly dividing cells
- Mutagenic and carcinogenic; can lead to secondary malignancies like acute leukemia
- Example: Cyclophosphamide used for Burkitt lymphoma and breast cancer
  - Adverse effects: Nausea, vomiting, myelosuppression, alopecia

Platinum coordination compounds

- Metal complexes
- Mechanism similar to alkylating agents
- Cisplatin used for neoplasms of testies, lymph tissue, or ovaries.
  - highly effective, but limited by nephrotoxicity
- Carboplatin used for ovarian cancers

Antimetabolites

- Structurally related to normal compounds within the cell
- Interfere with the availability of normal purine or pyrimidine nucleotide precursors
  - by inhibiting their synthesis
  - by competing with them in DNA or RNA synthesis
- Cell-cycle specific
- Their maximal cytotoxic effects are in the S-phase

Antimetabolites

- inhibit key metabolic steps required for DNA synthesis:
  -folic acid synthesis (e.g., methotrexate)
  -purine synthesis (e.g., mercaptopurine)
  -pyrimidine synthesis (e.g., fluorouracil)
- act during S phase of cell cycle
- some also used as immunosuppressive

Antimetabolites

- Methotrexate
- 6-Mercaptopurine
- 5-Fluorouracil
- Gemcitabine

- Adverse effects
  - Nausea, vomiting
  - Myelosuppression
  - Immunosuppression
  - Alopecia

Anticancer antibiotics

- Antitumor antibiotics interact with DNA causing disruption of DNA function → Cytotoxicity

- Mechanisms of cytotoxic effects
  - DNA intercalation
  - Inhibiting topoisomerases I and II
  - Producing free radicals

Anticancer antibiotics

- Bleomycin
- Doxorubicin
- Daunorubicin

Microtubule inhibitors

- Cause cytotoxicity by affecting the equilibrium between the polymerized and depolymerized forms of microtubules

- Vinblastine
  - Used for Hodgkin and non-Hodgkin lymphoma and acute lymphoblastic leukemia
- Vincristine
  - Used for Hodgkin and non-Hodgkin lymphoma and Metastatic testicular carcinoma
- Adverse effects of vinblastine and vincristine:
  - Nausea, vomiting, diarrhea
  - Phlebitis
  - Alopecia
  - Myelosuppression
  - Peripheral neuropathy

Steroid hormones and their antagonists

- Steroid hormone sensitive tumors are either
  1. Hormone responsive; tumor regresses following treatment with a specific hormone
  2. Hormone dependent; tumor regresses following removal of a hormonal stimulus
     - Can be accomplished by :
       - Surgery (e.g. orchiectomy for advanced prostate cancer)
       - Drugs (e.g. anti-estrogen for breast cancer)
  3. Both hormone responsive and hormone dependent

Prednisone

- Potent synthetic anti-inflammatory corticosteroid
- Use:
  - Treatment of lymphoma
- Adverse effects
  - Increased risk of infections due to immunosuppression
  - Ulcer
  - Hyperglycemia
  - Cataract formation
  - Osteoporosis
  - Mood changes
  - Hypertension

Tamoxifen

- Estrogen antagonist
- First line therapy for estrogen receptor responsive breast cancer
- Administered with a gonadotropin releasing hormone analog like leuprolide to lower estrogen levels in premenopausal women
- Adverse effects
  - Flashes
  - Nausea, vomiting,
  - vaginal bleeding
  - Can cause endometrial cancer

Aromatase inhibitors

- Aromatase catalyzes the production of estrogen from androstenedione in liver, fat, muscle, skin and breast tissue including breast malignancies
- Decrease the production of estrogen in postmenopausal women
- Anastrazole
  - Used for treatment of breast cancer in postmenopausal women

Leuprolide

- Analogs of gonadotropin releasing hormone
- Cause inhibition of secretion of LH and FSH
- This reduces androgen and estrogen synthesis
- Used for prostatic cancer and advanced breast cancer in premenopausal women
- Adverse effects
  - Impotence
  - Hot flashes

Estrogens

- Ethinyl estradiol and diethylstilbestrol
- Have been used for prostatic cancer
- Mechanism of action
  - Estrogens inhibit the growth of prostatic tissue by blocking the production of luteinizing hormone (LH)
  - This decreases the synthesis of androgens in testis
  - Affect tumors dependent on androgens
- Adverse effects
  - Thromboemboli
  - Myocardial infarction
  - Strokes
  - Gynecomastia
  - Impotence

Flutamide

- Antiandrogen
- Used for treatment of prostate cancer
- Androgen receptor antagonists, prevent the binding of natural hormone to the receptor
- Side effects
  - Gynecomastia
  - GI distress
  - Liver failure

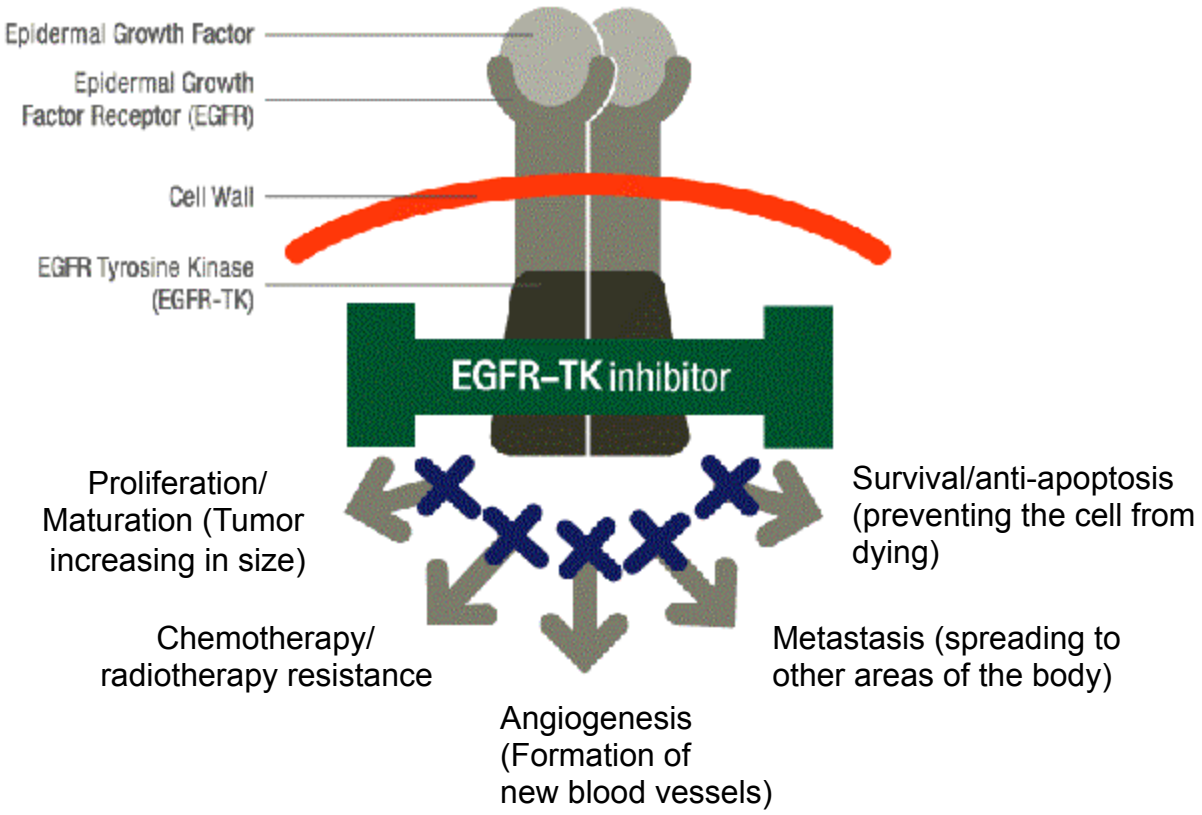
Tyrosine Kinases Receptors

- Transfer signals that direct
  - Growth
  - Division
  - Migration
  - Synthesis
  - Apoptosis (cell death)

EGFR expression in human tumors

- Invasion
- Metastasis
- Late-stage disease
- Chemotherapy resistance
- Hormone-therapy resistance
- Poor outcome

Strategies for TKR inhibitors



Tyrosine Kinase Inhibitors

- Gefitinib
  - Non-small cell lung cancer
  - Adverse effects: Skin rash, Diarrhea, Nausea/vomiting, myelosuppression
- Imatinib
  - Used for chronic myeloid leukemia
  - Adverse effects: Nausea, vomiting, hepatotoxicity

Monoclonal Antibodies

- Newer in drug development
- More directed at specific targets than other chemotherapeutic agents
- Associated with fewer side effects

- Bevacuzumab Anti VEGF monoclonal antibody
  - Approved as a first-line drug for metastatic colorectal cancer
  - Mechanism of action: Attaches to vascular endothelial growth factor (VEGF) and stops it from stimulating the formation of new blood vessels

- Cetuximab Anti EGFR monoclonal antibody
  - Approved to treat colorectal cancer
  - Targets epidermal growth factor receptor on the surface of cancer cells and interferes with their growth