Introduction to Anti-neoplastic Drugs

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Cancer

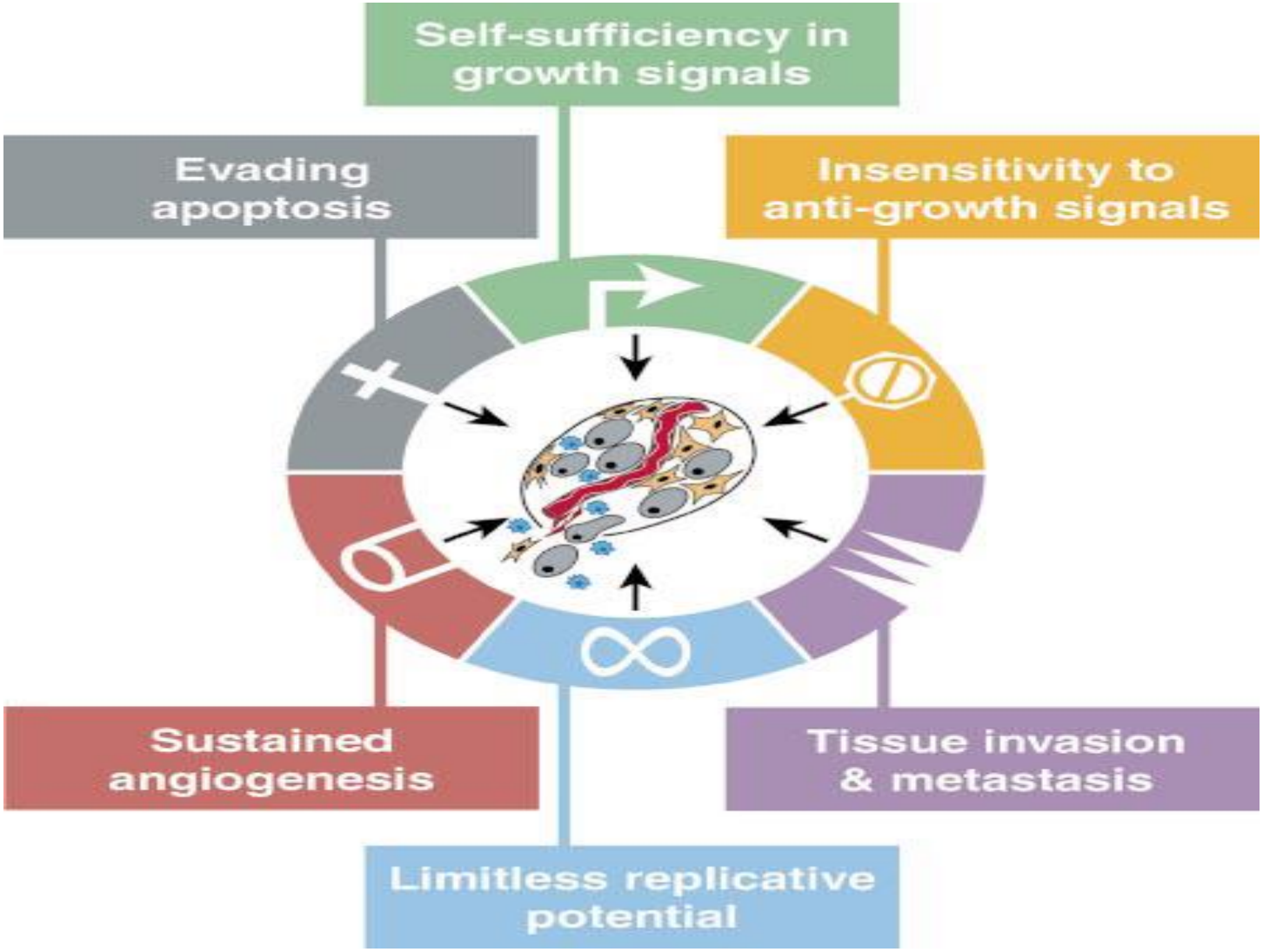
- Cancer is an abnormal and uncontrolled growth of cells caused by disruption in the normal controlling mechanisms that govern the balance between cell division, cell death and cell differentiation
- Tumours can be either:

1. Benign: Non-cancerous, rarely dangerous and grow locally

OR

2. Malignant: life-threatening and have the potential to invade locally, spread regionally and metastasize to distant sites in the body

The hallmarks of cancer



1. **Self-sufficiency in growth signals:**

A. Alteration of extracellular growth signals: PDGF in glioblastoma

B. Alteration of transcellular transducers of those signals: EGF-R/erbB) is overexpressed in stomach, brain, and breast tumors

C. Alteration of intracellular circuits that translate signals into action: N-myc gene in neuroblastoma

2. **Insensitivity to growth-inhibitory signals:** lose of TGF-b responsiveness

3. **Evading of apoptosis:** lose of p53 responsiveness

4. **limitless replicative potential:** Upregulation of telomerase enzyme

5. **Neoangiogenesis:** Overexpression of VEGF and VEGF receptors

6. **Tissue invasion and metastasis:** Overexpression of cell surface molecules that reduce cell-cell and cell-ECM interactions

Therapeutic methods to treat Cancer

1. **Surgery**

- It provides a means for diagnosis, accurate staging of disease and treatment by complete tumour resection

2. **Radiotherapy**

- Radiation therapy uses intense ionising radiation to kill cells and is a localised treatment targeted directly to the site of a tumour thereby avoiding damage to other tissues and minimising side-effects

3. Chemotherapy

- It is defined as' *the treatment of a disease by a chemical substance*' and is a systemic treatment which aims to inhibit tumour growth and/or induce cell death.
- Chemotherapy comprises of cytotoxic drugs that target DNA, RNA and protein in order to disrupt the cell cycle of rapidly dividing cells.
- They attack metabolic sites essential to cell replication e.g. purines & pyrimidines synthesis that are building blocks for DNA & RNA synthesis
- Anticancer drugs affect all proliferating cells both normal & abnormal cells

Purposes of chemotherapy

1. Primary treatment: Cytotoxic drugs is the primary curative modality for a few diseases, including leukemias, lymphomas, choriocarcinomas, and testicular cancer.
2. Palliative: Cytotoxic drugs is used to relieve symptoms and improve the quality of life in patients with advance stages of cancer.
3. Adjuvant: Use of Cytotoxic drugs to eradicate micrometastatic disease following localized modalities such as surgery or radiation or both.
4. Neoadjuvant: Use of cytotoxic drugs prior to surgery in an attempt to shrink the tumour

Chemotherapy used alone with curative intent

- Acute lymphocytic leukemia
- Acute nonlymphocytic (myelogenous) leukemia
- Burkitt's lymphoma
- Diffuse large cell lymphoma
- Hodgkin's lymphoma
- Testicular cancer
- Choriocarcinoma (gestational trophoblastic neoplasm)

Chemotherapy used as adjuvant therapy with curative intent

- Breast cancer
- Colorectal cancer
- Ewing's sarcoma
- Osteosarcoma
- Wilms' tumor
- Ovarian cancer

Chemotherapy used as neoadjuvant therapy

- Anal carcinoma[a]
- Bladder cancer
- Breast cancer (locally advanced)[a]
- Cervical cancer
- Esophageal cancer
- Head and neck cancers[a]
- Osteosarcoma[a]
- Rectal cancer
- Soft tissue sarcoma[a]

Chemotherapy used to palliate symptoms in advanced disease

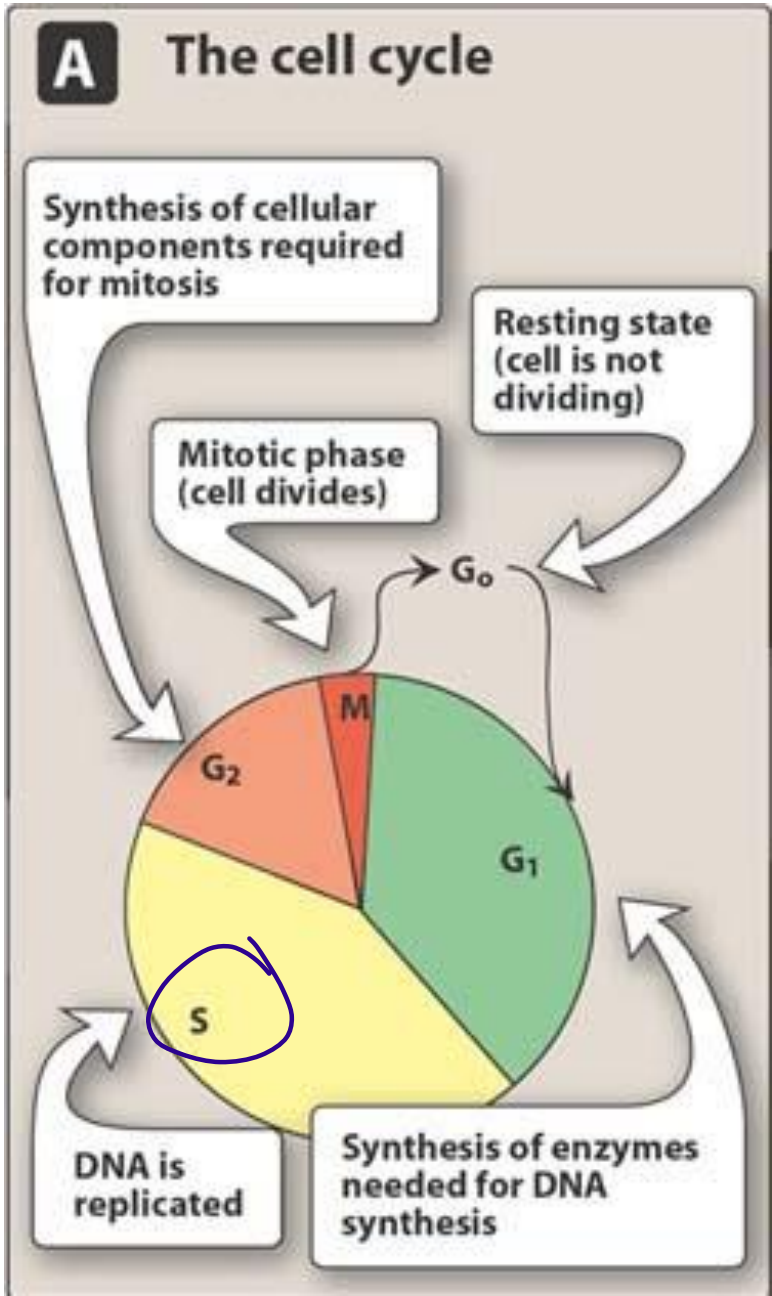
- Bladder cancer[a]
- Brain tumors
- Breast cancer[a]
- Carcinoid tumors
- Cervical cancer
- Chronic lymphocytic leukemia
- Chronic myelogenous leukemia[a]
- Colorectal cancer
- Endometrial cancer
- Esophageal cancer
- Gastric cancer
- Head and neck cancers
- Hairy cell leukemia[a]
- Kaposi's sarcoma
- Indolent lymphomas
- Metastatic melanoma
- Multiple myeloma[a]
- Mycosis fungoides
- Neuroblastoma[a]
- Non-small-cell lung cancer
- Osteosarcoma
- Ovarian cancer[a]
- Pancreatic cancer
- Prostate cancer
- Small cell lung cancer[a]
- Soft tissue sarcoma

Chemotherapy has little or no effect on palliation

- Hepatocellular cancer
- Renal cell carcinoma
- Thyroid cancer

Tumor susceptibility & growth cycle

- Both normal & tumor cells go through growth cycles but they differ in number of cells in each stage
- Tumours with a high percentage of S-phase cells are aggressively growing
- Most normal cells exist in the G0 phase, and most cancer cells are not sensitive to the effects of chemotherapy when in this stage.



- Tumour susceptibility to chemotherapeutic agents depends on the fraction of tumour cells that are in replicative cycle (Growth fraction)

لـ يعتمد على عدد الخلايا السرطانية الي داخله في Cell cycle

- Rapidly dividing cells are more sensitive to chemotherapeutic agents than slowly proliferating cells

- On this basis, Chemotherapeutic agents are classified as follows:

1. Cell-cycle specific (CCS) drugs :

- These act on cycling cells, and can produce their effect more on or selectively on particular phases of cell cycle.

- Examples:

  A. Anti-metabolites : inhibit DNA synthesis in S phase of cell cycle ;

  B. Vinca alkaloids: inhibit mitosis phase (M) of cell cycle in the metaphase stage

2. Cell-cycle non specific (CCNS) drugs :

- Are those with significant activity in multiple phases of cell cycle

- These destroy cells whether resting or dividing, but are more effective on rapidly dividing cells

- Examples are: Alkylating agents, cisplatin, nitrosoureas

COMBINATION CHEMOTHERAPY

- Cytotoxic agents with different toxicities, different molecular sites & mechanisms of action are usually combined at full doses

شروط انه نعمل Combination لازم تكون هذه الأدوية

- Advantages :

1. Provide maximal cell killing within range of tolerated toxicity, because of additive and/or potentiated cytotoxic effect
2. Are effective against broader range of cell lines

. Cells من مختلفة مجموعة عن مجموعة عبارة (tumor) لازم إنه حيث

3. May delay or prevent development of resistant cell lines

Strategies of combination chemotherapy

مثلاً بعطي 3 شايبج وبوقف بعدهم حتى نحسه، الخ.. وبعطي كمان 3 شايبج..

a. Pulse therapy : Involves intermittent cycles employing usually high doses of drugs are given for 3-4 weeks followed by rest non-drug period to allow hematologic and immunologic recovery

Cell cycle nonspecific drug

b. Recruitment : CCNS drugs are given first to get significant cell-kill ; this results in recruiting the remaining resting viable cells into cell cycle thus, CCS drugs are used then to get maximal cell-kill of recruited cells.

c. Synchrony : e.g. Vinca alkaloids are used to stop cell cycle at the mitosis phase , and are followed by S-phase specific drugs to get maximal cell-kill

- An example of combination chemotherapy is the common regimen called **POMP**

- POMP consists of Prednisone, Oncovin (vincristine), Methotrexate & Purinethol (mercaptopurine)

- POMP regimen is used for treatment of acute lymphocytic leukemia (ALL)

Problems associated with chemotherapy

1. **Resistance to chemotherapy:**

- It can be either:

A. Primary: inherent drug resistance; absence of response on the first exposure e.g. Melanoma

B. Acquired: develops after their use due to inadequate doses or duration of treatment.

- Resistance can be specific for a single drug or to many drugs (Multi-drug resistance MDR).

Mechanisms of resistance include the following:

A. Increased DNA repair: alkylating drugs and cisplatin

B. Decreased activation of pro-drugs: Decrease in activity of tumor cell enzymes needed to convert these drugs to cytotoxic metabolite e.g antimetabolites

C. Inactivation of effective drugs: Increased activity of enzymes capable of inactivating drugs e.g. antimetabolites

D. Changes in target enzyme: Decreased affinity or increased production of target enzymes for cytotoxic drugs e.g. DHFR

E. Formation of trapping agents: increased formation of trapping agents such as glutathione which interact with drug e.g. anthracyclines, bleomycin, and cisplatin

F. Decreased drug accumulation inside cancer cells : this usually causes multi-drug resistance and is due to increased formation of membrane P-170 glycoprotein that leads to increased efflux of many cytotoxic drugs out of cancer cells

2. Toxicity of chemotherapy:

1. **Acute effects**: nausea and vomiting

2. **Subacute or Delayed effects :**

A. **Bone marrow depression** : due to damage to stem cells or progenitors. This is a very important limiting factor in use of these drugs. It may result in :

1. **Leucopenia**
2. **Thrombocytopenia :** which may cause bleeding
3. **Anemia**
4. **Pancytopenia**

B. Immunosuppression : which also increases incidence of infections;

it is due to damage to both B-lymphocytes (which mediate immunity by differentiating into plasma cells that produce anti-bodies) and T-lymphocytes (which mediate cell-mediated immune reactions)

C. GIT damage: esp. to rapidly dividing epithelium causing mucositis that is seen as stomatitis, vomiting or diarrhea

D. Skin: esp. to hair follicles causing alopecia (usually temporary; hair re-grows again within 1 year)

E. Damage to gonads : This may cause sterility (esp. important in children), or mutations . Use in pregnancy is contra-indicated since they may cause abortion or teratogenesis

F. Delayed wound healing

G. Hyperuricemia : it is due to destruction of large number of tumour cells in sensitive cancers e.g. myeloma , CLL that leads to release of large amounts of nucleoproteins which ,after their metabolism, lead to increased uric acid formation from purines in liver.

H. Oncogenic effect : Second cancers (e.g. leukemia) have been reported few years after use of these drugs esp. alkylating agents and some anti-metabolites

I. Specific toxicity: May occur with many drugs.
Examples include:

Hepatic toxicity with 6-mercaptopurine,

Neurotoxicity with vincristine .

Hemorrhagic cysteitis with cyclophosphamide ,

Cardiac toxicity with the Anthracyclines ,

Lung toxicity with bleomycin or busulfan, and

Renal toxicity with cisplatin .

Contra-indications

a. Very advanced disease in debilitated patients

b. Active infection

c. Pre-existing bone marrow depression

d. Preganancy

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