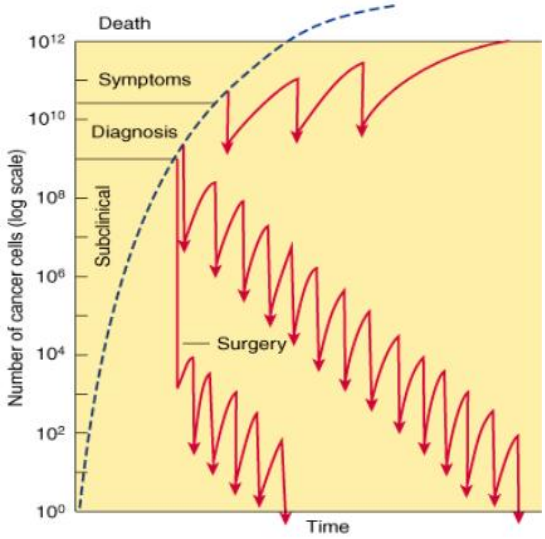
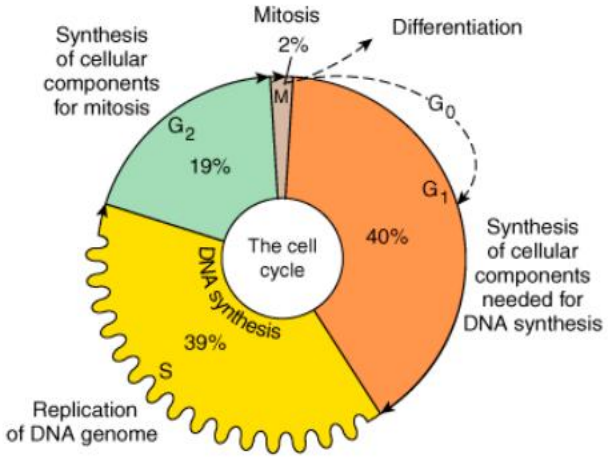
Unit I – Problem 9 – Pharmacology: Principles of Antineoplastic Chemotherapy

- **What is cancer?**
  - It is uncontrolled multiplication and spread within the body of abnormal forms of body's own cells.
- **What are the characteristics of a cancer cell?**
  - Uncontrolled proliferation.
  - De-differentiation (resulting in loss of function).
  - Invasiveness.
  - Metastasis.
- **Terminologies which are used:**
  - Anti-neoplastic drugs.
  - Anti-cancer drugs.
  - Cytotoxic drugs.
    Many of these drug are also used for disorders other than malignancies such as for autoimmune disorders and organ transplantation (for immunosuppression).
- **Log cell-kill hypothesis:**
  - A given antineoplastic drug kills constant fraction (but not constant number) of cells.
  - Cell kill is proportional regardless of the tumor burden.
  - Inverse relation between initial tumor cell number and remission or curability.



- **The cell cycle:**



- **Therefore, anti-neoplastic drugs can be:**
  - ✓ Cell-cycle specific drugs (S, G_1, M and G_2-specific).
  - ✓ Cell-cycle non-specific drugs.

- **Classes of anti-neoplastic drugs:**
  - Anti-metabolites (S-phase).
  - Topoisomerase-2 inhibitors (G1-S phases).
  - Taxanes (M-phase).
  - Vinca alkaloids (M-phase).
  - Anti-microtubular inhibitors (M-phase).
  - Anti-tumor antibiotics (G_2-M phases).
  - Alkylating agents.
  - Anthracyclines.
  - Anti-tumor antibiotics.
  - Camptothecins (topoisomerase inhibitors).
  - Platinum analogs.
- **General approaches to cancer management:**
  - **The main goal is total cell kill of malignant cells via:**
    - ✓ Surgical removal.
    - ✓ Radiation ablation.
    - ✓ Chemotherapy: which can be curative or palliative (مخفِّف للأعراض).
    - ✓ Management of treatment-related complications.
    - ✓ Multimodality/ combination treatment (why?):
      - ❖ Improving efficacy.
      - ❖ Decreasing toxicity.
      - ❖ Optimum scheduling intervals.
      - ❖ Targeting different molecular mechanisms.
      - ❖ Transition between drug schedule changes.
      - ❖ Reducing drug resistance.
  - **Newer targets for drugs:**
    - ✓ Inactivation of components of oncogen signaling pathway which is represented by:
      - ❖ Inhibition of growth factor receptors.
      - ❖ Inhibition of cytoplasmic kinases, cyclins and cyclin-dependent kinases.
      - ❖ Antisense nucleotides.
      - ❖ Inhibition of antiapoptotic or stimulation of pro-apoptotic factors.
    - ✓ Restoring functions of tumor suppressor genes via:
      - ❖ Gene therapy.
    - ✓ Employing tissue-specific proliferation inhibition via:
      - ❖ Hormones and hormone antagonists.
    - ✓ Inhibition of tumor growth, invasion and metastasis via:
      - ❖ Inhibition of angiogenesis.
      - ❖ Inhibition of matrix metalloproteases.
    - ✓ Enhancing the immune response of the host through:
      - ❖ Cytokine therapies.
      - ❖ Gene therapies.
- **Antineoplastic drug resistance:**
  - **How does it develop?**
    - ✓ Decreased accumulation of the drug (e.g. efflux of the drug through P-glycoproteins).
    - ✓ Decreased conversion of prodrug into active drug.
    - ✓ Development of an alternative metabolic pathway.
    - ✓ Altered target protein by genetic mutation.

- **Chemotherapy uses:**

Primary induction treatment	Chemotherapy in advanced stages of cancer for which alternatives are not available as a palliative therapy
Neo-adjuvant treatment	Chemotherapy in patients with localized cancer for which alternative local therapy (such as surgery) exist but is less effective. Often, radiotherapy and chemotherapy are used concurrently or alternately
Adjuvant treatment	Chemotherapy to reduce the incidence of both local and systemic recurrence and to improve overall survival

- **Classification of anticancer drugs:**

Inhibitors of thymidylate synthase	5-Fluorouracil
Inhibitors of purine metabolism	6-Mercaptopurine
Inhibitors of ribonucleotide reductase	Hydroxyurea
Purine or pyrimidine analogs	Incorporated into DNA: thioguanine and cytarabine
Agents that directly modify DNA structure	• Alkylating agents: cyclophosphamide • Platinum compounds: carboplatin • Bleomycins: bleomycin
Topoisomerase inhibitors	• Campothecins: irinotecan • Anthracyclines: doxorubicin • Epipodophyllotoxins: teniposide
Microtubule inhibitors	• Vina alkaloids: vincristine • Taxanes: paclitaxel
Hormones	• Corticosteroids: prednisone • Estrogens and anti-estrogens • Androgens and anti-androgens • LHRH-antagonists
Miscellaneous	Newly developed, more selective, mostly biologic response modifiers (including humanized monoclonal antibodies)
Targets for new drugs	• Growth factors and growth factor receptors (trastuzumab and cetuximab). • Intracellular signal transduction pathways (imatinib and nilotinib). • Angiogenesis.

- **Limitations of these drugs:**
  - ✓ Limited selective toxicity and narrow therapeutic index.
  - ✓ Nausea and vomiting are common adverse reactions.
  - ✓ Hyperuricemia (increased uric acid due to increased cell turnover), teratogenicity and carcinogenicity are possible.
  - ✓ Myelosupression (inhibition of the bone marrow) is the most critical adverse reaction leading to: bleeding, infections and anemia.