ANTICANCER DRUGS

Chemotherapeutic agents used to treat malignancies or to control the growth of cancerous cells. Drug therapy may be used alone, or in combination with other treatments such as surgery and/or local radiation therapy.

PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer chemotherapy strives to cause lethal cytotoxic event or apoptosis in the cancer cells that can arrest a tumor’s progression. Many of the most effective cytotoxic agents act by damaging DNA (fig.1) and other agents act against metabolic sites essential to cell replication. Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most of current available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds proliferating cells, both normal and abnormal. One of the characteristics that distinguish anticancer drugs from other drugs is the frequency and severity of side effects at therapeutic doses.
A. Treatment Strategies

1. Goals of treatment: The ultimate goal of chemotherapy is a cure (disease-free survival). A true cure requires eradication of every neoplastic cells. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading). In advance stages of cancer when the control is far from reality then the goal is palliation (alleviation of symptoms and avoidance of life-threatening toxicities).
2. **Indications for treatment**: Chemotherapy is sometimes used when neoplasms are disseminated and are not amenable to surgery.

- **Adjuvant chemotherapy**: Using of chemotherapy as a supplemental treatment to attack micrometastases following surgery and radiation treatment.

- **Neoadjuvant chemotherapy**: Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer.

- **Maintenance chemotherapy**: Chemotherapy given in lower doses to assist in prolonging a remission.

3. **Tumor susceptibility and the growth cycle**: Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas nonproliferating cells (those in G0 phase) usually survive the toxic effect of these agents.

- **Cell-cycle specificity of drugs**: Both normal cells and tumor cells go through a growth cycle. Chemotherapeutic agents are effective only in replicating cells, that is those cells that are cycling, are said to be cell-cycle specific. Whereas other agents are cell-cycle nonspecific.
- Tumor growth rate: The growth rate of most tumors in vivo is initially rapid, but decreases as the tumor size increases because of the unavailability of nutrients and oxygen due to inadequate vascularization. Reducing the tumor burden through surgery or radiation promotes the recruitment of the remaining cells into active proliferation and increases their susceptibility to chemotherapeutic agents.

B. Treatment regimens and scheduling

Drug dosages are usually calculated on the basis of body surface area, in an effort to tailor the medications to each patient.

- Log kill phenomenon: Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics (that is, a given dose of drug destroys a constant fraction of cells). The term log kill is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about $10^9$ (total) leukemic cells. Consequently, if treatment leads to 99.999% kill, then 0.001% of total leukemic cells ($10^4$) remain; this is equivalent to 5-log kill. At this point the patient is asymptomatic, that is the patient in remission. Additional treatment is required to totally eradicate the leukemic cells.

- Pharmacologic sanctuary: Leukemic or other tumor cells find sanctuary in tissues; an area that is poorly penetrated by pharmacological agents and therefore is the place in which cancer cell can escape the effects of drug therapy. for example CNS.
- Treatment protocols: Combination drug chemotherapy is more successful than single-drug treatment in most of the cancers for which chemotherapy is effective.

**Advantages of chemotherapy drugs combination:**

1. Provide maximal cell killing within the range of tolerated toxicity.
2. Are effective against a broader range of cell lines in the heterogeneous tumor population.
3. May delay or prevent the development of resistant cell lines.

**C. Problems associated chemotherapy**

1. Resistance: Prolonged administration of suboptimal drug doses may lead to mutation and producing resistant cancer cells.
2. Multidrug resistance: This resistance is due to ATP dependent pumping of drugs out of the cells in the presence of P-glycoprotein.

(Fig.3) Pumping chemotherapies out of the cells by P-glycoprotein

3. Toxicity: Normal cells undergoing rapid proliferation (for example, cells of buccal mucosa, bone marrow, GI mucosa, and hair follicles) are affected by chemotherapies.
4. Treatment-induced tumor: Because most antineoplastic agents are mutagens, neoplasm may arise 10 years or more after the original cancer was cured.