**Oncolog Rotation Manual**

**Pharm.D programme 2016**

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**PRINCIPLES OF ONCOLOGY:**

The term *cancer* refers to a heterogeneous group of diseases caused by an impairment of the normal functioning of genes, which leads to genetic damage.

Cancer cells are also referred to as tumors or neoplasms

**Characteristics of cancer cells:**

a) uncontrolled growth (prolefration) B) divide rapidly c) non-functional d) invasive e) metastasis

 **Types of cancer:**

Tumors can be benign or malignant. **Benign** tumors are generally slow growing, resemble normal cells, are localized, and are not harmful. **Malignant** tumors often proliferate more rapidly, have an atypical appearance, invade and destroy surrounding tissues, and are harmful if left untreated

 **Malignant cancers** are further categorized by the location from where the tumor cells arise.  **A) Solid tumors**: **Carcinomas** are tumors of epithelial cells. These include specific tissue cancers (e.g., lung, colon, breast). **Sarcomas:** include tumors of connective tissue such as bone (osteosarcoma) or muscle (e.g., leiomyosarcoma).

**B**) **Hematological malignancies. Lymphomas** are tumors of the lymphatic system and include Hodgkin and non-Hodgkin lymphomas. Leukemias are tumors of blood-forming elements and are classified as acute or chronic and myeloid or lymphoid**.**

**Incidence.** Cancer is the **second leading cause of death** in the United States. The most common cancers are breast, prostate, and colorectal. The leading cause of cancer death is lung cancer

**Precipitating factors for CANCER (Carcinogenesis) :**

1. Viruses: Epstein-Barr virus (EBV), hepatitis B virus (HBV), and human papillomavirus (HPV)
2. Environmental and occupational exposures: benzene , radiation.
3. Life style : high fatty meals (gastric cancer), alcohol (liver CA),
4. Age & Gender : incidence is higher with increasing age
5. Drugs : alkylating agents may cause second malignancy
6. Bacteria : H-pylori increase the risk of Gastric CA
7. Genetic factors

NOTE :

 there are two major classes of genes involved in cancer: **1) Oncogenes** **:** Protooncogenes are normal genes that, through some genetic alteration caused by carcinogens, change into **oncogenes**. The oncogene produces abnormal or excessive gene product that disrupts normal cell growth and proliferation

EX:

1. *K-RAS* : Involved in lung, ovarian, colon, and pancreatic cancer
2. *N* – RAS involved in leukimias
3. *EGFR*: Codes for epidermal growth factor Receptor involved in Glioblastoma, breast cancer, squamous carcinoma
4. *PDGF*: Codes for platelet-derived growth factor involved in glioma (brain CA)
5. *HER-2* : involved in Breast, prostate, bladder and ovarian cancers

**2) tumor-suppressor gene:** inhibit inappropriate cellular growth and proliferation by gene loss or mutation**.** The *p53* gene is one of the most common tumor-suppressor genes, andmutations of *p53* may occur in up to 50% of all malignancies. This gene stops the cell cycle to enable “repairs” of the cell. If *p53* is inactivated, then the cell allows the mutations to occur. Other tumor suppressor gene: BRCA1 , BRCA2, NF-1, RB-1

**Prevention :**

1. Decrease uptake of carcinogens
2. Achieving ideal body weight
3. Smoking cessation
4. Avoid sun exposure
5. Increase anti oxidants intake such as vit A,C,E Green tea,Zinc.
6. Decrease fat diet and red meat.
7. Increase fiber intake (vegetables & fruits)
8. Low dose aspirin has a role in prevention of colon CA.

Assignment 1:

M.S., a 37-year-old woman, asks about taking medications to reduce her risk of cancer. Her mother died several years ago of colon cancer, and she fears that she also will develop the disease. Does taking anti-inflammatory medications alter the risk of cancer?

**Detection** and **diagnosis**:

are critical for the appropriate treatment of cancer. Earlier detection may improve response to treatment.

1. **Warning signs** of cancer have been outlined by the **American Cancer Society**.

 General signs and symptoms of cancer may include : unexplained weight loss, fever, fatigue, pain, and skin changes. Signs and symptoms of specific types of cancer can include changes in bowel habits or bladderfunction, a sore that does not heal, white patches or spots in the mouth or on the tongue, unusual bleeding or discharge, thickening or lump in the breast or other body part, indigestion or difficulty swallowing, nagging cough or hoarseness.

**2.Guidelines for screening:**

Please refer to the following guide lines *a) American Cancer Society* b) the National Cancer Institute

**3) Tumor markers**

are biochemical indicators of the presence of neoplastic proliferation detected in serum, plasma, or other body fluids. These tumor markers may be used initially as screening tests, to reveal further information after abnormal test results, or to monitor the efficacy of therapy. Elevated levels of these markers are not definitive for the presence of cancer because levels can be elevated in other benign and malignant conditions, and false-positive results do occur. Examples of some commonly used markers include the following:

**a.** Carcinoembryonic antigen (CEA) for colorectal cancer normal <5ng/ml high > 10ng/ml

**b.**alphaFetoprotein (AFP) for hepatocellular CA or hepatoblastoma normal <10ng/ml high >200 ng/ml

**c.** Prostate-specific antigen (PSA) for prostate cancer normal <4ng/ml high >10ng/ml

**others .**CA-125 for ovarian CA, CA15-3 for breast CA, B-HCG for testicular cancer .

 **4)Tumor biopsy.**

 The definitive test for the presence of cancerous cells is a biopsy and pathological examination of the biopsy specimen.

1. **Imaging studies**,

 such as radiograph, CT scans, MRI, and positron emission tomography (PET), may be used to aid in the diagnosis or location of a tumor and to monitor response to treatment .

**6)** **Other laboratory tests**

a) commonly used for cancer diagnosis include complete blood counts (CBCs) and blood chemistries. A CBC measures the levels of the three basic blood cells—white cells, red cells, and platelets

.

b) The CBC will often include an absolute neutrophil count (ANC), which measures the absolute number of neutrophils in a person’s white blood count.

**c) The ANC is calculated by multiplying the white blood count (WBC) \* total neutrophil count \* 10**

**7) Staging** is the categorizing of patients according to the extent of their disease. The stage of the disease is used to determine prognosis and treatment. In adult patients with cancer, two different staging systems are widely employed for the staging of neoplasms

**1)TNM classification:**

**a.** *T* indicates tumor size and is classified from 0 to 4, with 0 indicating the absence of tumor.

**b.** *N* indicates the presence and extent of regional lymph node spread and is classified from 0 to 3, with 0 indicating no regional lymph node involvement and 3 indicating extensive involvement.

**c.** *M* indicates the presence of distant metastases and is classified as 0 (for absence) or 1 (for presence of distant metastases).

**d.** For example, T2N1M0 indicates a moderate-size tumor with limited nodal disease and no distant metastases

2) **AJCC** staging, developed by the American Joint Committee on Cancer, classifies cancers as stages 0 to IV. An assigned TNM translates into a stage. A high number indicates larger tumors with extensive nodal involvement and/or metastasis. Generally, high numbers also indicate a worse prognosis. There are specific staging criteria for each tumor type.

**Rx modalities**

1. surgery
2. radiation
3. chemotherapy
4. biological therapy

**Malignancies Frequently Treated With Radiation Therapy**

1)Acute lymphocytic leukemia (CNS radiation)
2) Brain tumors
3) Breast cancer
4) Head and neck cancers, squamous cell
5) Lung cancer

6) Prostate cancer
7) Rectal cancer

**Common Cancers and Sites of Metastases**

|  |  |
| --- | --- |
| * Breast
 |   |
| * Premenopausal
* Postmenopausal
 | Lymph nodes, skin, lung, liver, bone, brainLymph nodes, bone, soft tissue |

|  |  |
| --- | --- |
| * Colon
 |  Lymph nodes, liver, lung, ovary, bone |
| * Lung
 |  |
| * Non–small-cell
* Small-cell
 |  Lymph nodes, liver, bone, brain, adrenals Lymph nodes, bone, liver, bone marrow, brain |

* Lymphomas
* Hodgkin lymphoma Liver, spleen, stomach, bone marrow, lung
* Non-Hodgkin bone marrow, liver, lung ,GIT,CNS
* Ovary Peritoneum, lung

|  |  |
| --- | --- |
| * Prostate
 |  Lymph nodes, bone, liver |
|  |  |

**CELL LIFE CYCLE**

Knowledge of the cell life cycle and cell cycle kinetics is essential to the understanding of the activity of chemotherapy agents in the treatment of cancer.

**Phases of the cell cycle**

**1. M phase**, or **mitosis**, is the phase in which the cell divides into two daughter cells.

**2. G**1 **phase**, or **postmitotic gap**, is when RNA and the proteins required for the specialized functions required for the specialized functions

**3. S phase** is the phase in which DNA synthesis and replication occurs.

**4. G**2 **phase**, or the **premitotic** or **postsynthetic gap**, is the phase in which RNA and the enzymes topoisomerase I and II are produced to prepare for duplication of the cell.

**5. G**0 **phase**, or **resting phase**, is the phase in which the cell is not committed to division. Cells in this phase are generally not sensitive to chemotherapy. Some of these cells may reenter the actively

dividing cell cycle. In a process called **recruitment**, some chemotherapy regimens are designed to enhance this reentry by killing a large number of actively dividing cells



**Cell growth kinetics.** Several terms describe cell growth kinetics.

**1. Cell growth fraction** is the proportion of cells in the tumor dividing or preparing to divide. As the tumor enlarges, the cell growth fraction decreases because a larger proportion of cells may not be able to obtain adequate nutrients and blood supply for replication.

**2. Cell cycle time** is the average time for a cell that has just completed mitosis to grow and again divide and again pass through mitosis. Cell cycle time is specifi c for each individual tumor.

**3. Tumor doubling time** is the time for the tumor to double in size. As the tumor gets larger, its doubling time gets longer because it contains a smaller proportion of actively dividing cells owingo restrictions of space, nutrient availability, and blood supply

**Tumor cell burden** is the number of tumor cells in the body.

**1.** Because a large number of cells is required to produce symptoms and be clinically detectable (approximately 109 cells), the tumor may be in the plateau phase of the growth curve by the time it is discovered.

**2.** The **cell kill hypothesis** states that a certain percentage of tumor cells will be killed with each course of cancer chemotherapy.

**a.** As tumor cells are killed, cells in **G**0 may be recruited into **G**1, resulting in tumor regrowth.

**b.** Thus, repeated cycles of chemotherapy are required to achieve a complete response or remission

**Chemotherapeutic Agents:**

Chemotherapeutic agents may be classified according to their **reliance on cell cycle kinetics** for their cytotoxic effect. Combinations of chemotherapy agents that are active in different phases of the cell cycle may result in a greater cell kill.

**1. Phase-specific agents** are most active against cells that are in a specific phase of the cell cycle. These agents are most effective against tumors with a high growth fraction. Theoretically, administering these agents as continuous intravenous infusions or by multiple repeated doses may increase the likelihood of hitting the majority of cells in the specific phase at any one time. Therefore, these agents are also considered schedule-dependent agents. Examples are as follows:

**a.** M phase: mitotic inhibitors (e.g., vinca alkaloids, taxanes)

**b. G**1 phase: asparaginase, prednisone

**c.** S phase: antimetabolites

**d. G**2 phase: bleomycin, etoposide

**2.Phase-nonspecific agents** are effective while cells are in the active cycle but do not require that the cell be in a particular phase. These agents generally show more activity against slow-growing tumors. They may be administered as single bolus doses because their activity is independent of the cell cycle. These drugs are also considered dose-dependent agents. Examples are alkylating agents and antitumor antibiotics.

**3. Cell cycle–nonspecific agents** are effective in all phases, including **G**0. Examples are carmustine and lomustine. Radiation therapy is also considered cell cycle nonspecific.

**Objectives of chemotherapy**

**1. For cancers like leukemias and lymphomas, several phases of chemotherapy are necessary**. A **cure** may be sought with aggressive therapy for a prolonged period to eradicate all disease. For leukemias, this curative approach may consist of the following components:

**a. Remission induction**: therapy given with the intent of maximizing cell kill.

**b. Consolidation** (also known as intensification or post-remission therapy): therapy to eradicate any clinically undetectable disease and to lower the tumor cell burden below 103, at which level host immunological defenses may keep the cells in control.

**c. Maintenance**: therapy given in lower doses with the aim of maintaining or prolonging a remission.

**2.For solid tumors,** one or more approaches to chemotherapy may be used when seeking a cure based on the known utility of chemotherapy in line with other modalities, such as surgery or radiation.

**a. Adjuvant** chemotherapy is given after more definitive therapy, such as surgery, to eliminate any remaining disease .

**b. Neoadjuvant** chemotherapy is given to decrease the tumor burden before definitive therapy, such as surgery or radiation.

**Chemotherapy dosing**

may be based on body **weight**, body surface area (**BSA**), or area under the concentration versus time curve (**AUC**). BSA is most frequently used because it provides an accurate comparison of activity and toxicity across species

**Combination chemotherapy**

is usually more effective than single-agent therapy.

**1.** When combining chemotherapy agents, factors to consider include

**a.** Antitumor activity

**b.** Different mechanisms of action

**c.** Minimally overlapping toxicities

**2.** The reasons for administering combination chemotherapy include

**a.** Overcoming or preventing resistance

**b.** Cytotoxicity to resting and dividing cells

**c.** Biochemical enhancement of effect

**d.** Rescue of normal cells

**3. Dosing** and **scheduling** of combination regimens are important because they are designed to allow recovery of normal cells. These regimens generally are given as short courses of therapy in cycles.

Note: **Acronyms** often are used to designate chemotherapy regimens. For example, CMF refers to a combination of cyclophosphamide, methotrexate, and fluorouracil used in the treatment of breast cancer.

**Administration**

**Routes** of administration vary depending on the agent and the disease state. Although intravenous (IV) administration is most commonly employed, oral administration of chemotherapy is becoming increasingly more common.

Other administration techniques include oral, subcutaneous, intrathecal, intra-arterial, continuous IV infusion, bolus IV infusion.

Drugs that may be given **intrathecally** include methotrexate, cytarabine, and hydrocortisone.

Drugs should not be administered by the intrathecal route without specific information supporting intrathecal administration. administration of vinca alkaloids (e.g. **vincristine**) by the intrathecal route results in ascending paralysis and **death.**

Products with different formulations, including liposomal or pegylated agents (e.g., liposomal doxorubicin), are being used to decrease frequency of administration and/or reduce toxicities

**Response to chemotherapy**

**Complete response** (**CR**) indicates disappearance of all clinical, gross, and microscopic disease.

**PR** indicates a greater than 50% reduction in tumor size, lasting a reasonable period. Some evidence of disease remains after therapy.

**TOXICITY OF ANTICANCER DRUGS**

Rapidly proliferating cells such as the bone marrow, GI tract mucosa, hair follicles are most sensitive to cytotoxic drugs.

Most often bone marrow supression (BMS) is dose-limiting. Anticancer drug dosage is usually carefully titrated to avoid excessive neutropenia (granulocytes <50O/dL) and thrombocytopenia (platelets <20,00o/dL); colony stimulating factors, erythropoietin, and thrombopoietin can be supportive -🡪 decrease risk of infections and need for antibiotic

