



Applied Therapeutics–II

Cancer Chemotherapy & Treatment

Lecture-?

الموضوعات المقررة	
cancer prevention	Non pharmacological therapy
carcinogenesis	Pharmacological therapy
metastases	Dosing of chemotherapy
pathophysiology	Combination chemotherapy
Desired outcomes	

Level: 5th
Semester: 2nd

Reference: pharmacotherapy principles and practice

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Cancer chemotherapy & treatment

Cancer (neoplasm, tumor, or malignancy) is a group of diseases (> 100 disease) *characterized by*

1. uncontrolled cellular growth,
2. tissue infiltration, and
3. spread of abnormal cells (can't carry out normal physiological functions).

Cancer Prevention:

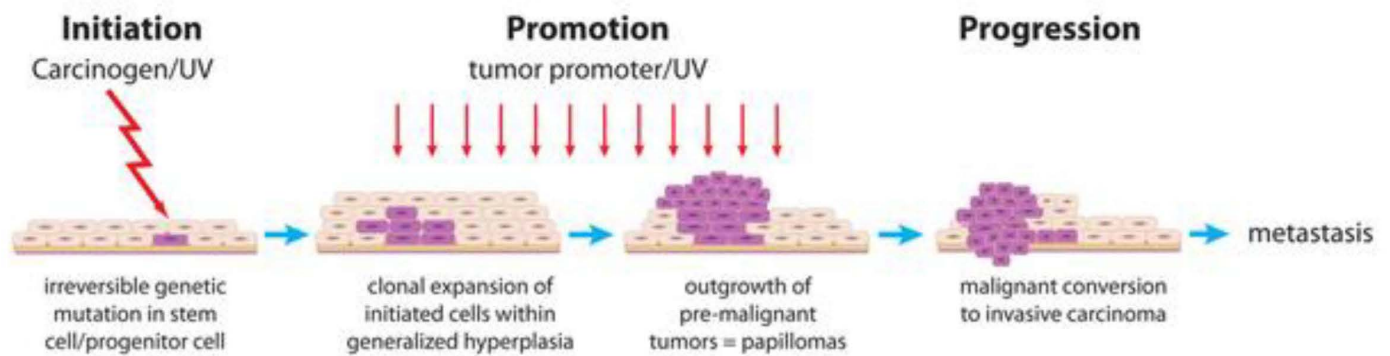
- Most cancers are **not curable** in *advanced stages*.
- Both lifestyle modifications and chemoprevention agents may significantly **reduce** the **risk** of developing cancer.
- The Food and Drug Administration (FDA) has approved vaccines that can help prevent cancer. Available vaccines include those that prevent infection with human papillomavirus (HPV), responsible for cancers of the cervix, vulva, vagina, and anus and a vaccine that prevents hepatitis B viral infections, which can cause liver cancer.

Cancer Prevention continue

- Additionally, **medications**, such as the selective estrogen receptor modulator (SERM) tamoxifen reduces the risk of breast cancer in premenopausal women, **while** raloxifene and aromatase inhibitor (AI) exemestane reduce breast cancer in high-risk postmenopausal women. Because of **possible long-term** complications (eg, an increased risk of endometrial cancer with the use of tamoxifen) benefits versus risks needs to be weighed when making a recommendation.
- **Smoking cessation** is associated with a gradual decrease in the risk of cancer (e.g., lung, pharynx, mouth and esophageous), but more than 5 years is needed before a major decline in risk is detected.
- Proper **sun protection**, including minimizing sun exposure, using sunscreens with a sun protection factor (SPF≥15) on exposed areas, wearing protective clothing and sunglasses, avoiding tanning beds and sun lamps, can help in preventing the risk of skin cancer.

CARCINOGENESIS

- Carcinogenesis is the process by which normal cells are transformed into cancer cells.
- The exact cause of cancer remains **unknown** and is **probably very diverse**. It is thought that cancer develops from a single cell in which the normal mechanisms for control of growth and proliferation are **altered**.
- Evidence indicates that there are **4 stages in the cancer development** process.
 1. The **first** step, **initiation**, occurs when a carcinogenic substance encounters a normal cell to produce genetic damage and results in a mutated cell.
 2. The environment is altered by carcinogens or other factors to favor the growth of the mutated cell over the normal cell during **promotion**. (**reversible process**)
 3. Third, **transformation** (or **conversion**) occurs when the mutated cell becomes malignant
 4. Finally, **progression** occurs when cell proliferation takes over and the tumor **spreads** or develops **metastases**.



CARCINOGENESIS : Continue

- ❑ There are **two major classes** of **genes** involved in **carcinogenesis**, **oncogenes** and **mutation of tumor suppressor genes** (eg. **p53** gene).
 - A. **Protooncogens** are **normal genes** present in cells that **converted by carcinogenic substances** (eg. **Smoking or radiation**) into **oncogene**.
 - B. **Tumor suppressor genes (p53)** are **normal genes** which have **protective effects against oncogenes**. They **inhibit inappropriate cellular growth and proliferation**.

Carcinogenic substances:

1. **Chemicals**, such as **aniline** and **benzene**, are associated with the development of **bladder cancer** and **leukemia**, respectively.
2. **Environmental** factors, such as excessive **sun exposure**, can result in **skin cancer**, and **smoking** is widely known as a cause of **lung cancer**.
3. **Viruses**, including **HPV**, **Epstein-Barr virus**, and **hepatitis B virus**, have been linked to **cervical cancers**, **lymphomas**, and **liver cancers**, respectively.
4. **Anticancer agents** such as the **alkylating agents** (eg, **melphalan**), **anthracyclines** (eg, **doxorubicin**), and **epipodophyllotoxins** (eg, **etoposide**) can cause **secondary malignancies** (eg, **leukemias**) years after therapy has been completed.

Note: The patient's **age**, **gender**, family **history**, **diet**, and chronic **irritation** or **inflammation** may be considered to be **promoters** of carcinogenesis.

Metastases:

نمو نفس نوع الخلية السرطانية على مسافة ما من موقع الورم الرئيسي

- ☐ A metastasis is a **growth of the same cancer cell** found at some **distance from the primary tumor site**. The presence of metastasis at diagnosis usually is associated with a poorer prognosis than the patient with no known metastatic disease. Usually, **once distant metastases have occurred**, the cancer is considered **incurable**. لا أمل في علاجه
- ☐ Cancers **spread** usually by **two pathways**:
 1. **Hematogenous** (through the **bloodstream**) or through the
 2. **Lymphatics** (drainage through adjacent **lymph nodes**).
- ☐ The usual **metastatic sites for solid tumors** are **brain**, **bone**, **lung**, and **liver**.

PATHOPHYSIOLOGY

❖ Tumor Origin

- Tumors may arise from the **4 basic tissue types**: **Epithelial (carcinoma)**, **Connective** (ie, muscle, bone, & cartilage) (called **sarcoma**), **Lymphoid**, or **Nerve** tissue.
- **Adenocarcinomas** arise from **glandular** tissue (eg. Lung, breast, colon, ...) .
- **Malignancies** of the bone marrow or lymphoid tissue, such as leukemias or lymphomas, are **named differently**.
- The suffix **-oma** is added to the name of the cell type if the tumor cells are **benign** (eg. Lipoma).
- Precancerous cells have cellular changes that are abnormal but not yet malignant and may be described as **hyperplastic** or **dysplastic**.

❖ Tumor Characteristics

- Tumors are either **benign** or **malignant**.
- **Benign tumors** often are **encapsulated**, **localized**, and **indolent**; they **seldom metastasize**; and they **rarely recur once removed**.
مغلقة في محلها/مكانها ؛ نادرا ما ينتقل الى مكان اخر. ونادرا ما تتكرر بمجرد إزالتها
- **Malignant** tumors are **invasive** and **spread** to other locations even if the primary tumor is removed. The cells no longer perform their usual functions, and their cellular architecture changes (**anaplasia**).
تخترق وتنتشر إلى مواقع أخرى حتى لو تمت إزالة الورم الرئيسي. لا تؤدي وظائفها المعتادة ، وتغيرت بنيتها الخلوية

TREATMENT

Desired Outcome

- **Chemotherapy** may be given to **cure** cancers, **or** it may be given to help **control the symptoms** of an incurable cancer (also known as **palliation**).
- **Palliative care** consists of **pharmacologic and nonpharmacologic treatments** and is **most effective** when initiated at the time of other treatments, improving quality of life.

Treatment of cancer

- The **three primary treatment** modalities of cancer are **surgery**, **radiation**, and **pharmacologic** therapy.

Non-pharmacological therapy of cancer

- **Surgery** is useful to gain tissue for diagnosis of cancer and for treatment, especially those cancers with limited disease. **However**, when cancer is widespread, **surgery** may play little or **no role**, but **radiation** therapy localized to specific areas may **palliate symptoms**.
- **Radiation** plays a key **role** not only in the treatment and possible cure of cancer but also in palliative therapy
- ❖ **Together**, **surgery and radiation** therapy may provide local control of symptoms of the disease.

Pharmacological therapy of cancer

- 1- **Adjuvant therapy:** Systemic therapies that administered after surgery to destroy microscopic malignant cells (*surgery can remove all macroscopic but not all microscopic disease*).
 - The **goals** of adjuvant chemotherapy are **to decrease the recurrence** by eliminating microscopic malignant cells of the cancer and to **prolong survival**.
- 2- **Neo-adjuvant chemotherapy:** Chemotherapy that is given before surgical resection of the tumor **to decrease the tumor burden** to be removed and make the **surgery easier** to perform because the tumor has **shrunk away from vital organs or vessels**. انكماش/تقلص الورم بعيداً عن الأعضاء الحيوية أو الأوعية.

Dosing of Chemotherapy

- Chemotherapeutic agents typically have a **very narrow therapeutic index**.
- The **doses** of chemotherapy must be given at a **frequency** that **allows the patient to recover from the toxicity of the chemotherapy**; **each period** of chemotherapy dosing is referred to as a **cycle**.
- Each cycle of chemotherapy may have the **same dosages**; the **dosages may be modified based on toxicity**; **or** a chemotherapy **regimen** may **alternate** from **one set of drugs** given during the **first, third, and fifth cycles** **to another set** of **different** drugs given during the **second, fourth, and sixth cycles**.
- The **dose density** of chemotherapy **refers to shortening of the period between cycles** of chemotherapy. Administration of dose-dense chemotherapy regimens often **used when goal of therapy is cure** and it requires the use of **colony-stimulating factors** (eg, **Filgrastim** or **granulocyte-colony stimulating factor [G-CSF]**) **to be administered to shorten neutropenia duration & severity**.
- **When a chemotherapy regimen is used as Palliation** (to control symptoms), the **dosages** of chemotherapy may be **decreased based on toxicity** **or** the **interval between cycles** may be **lengthened** to maintain quality of life.
- **Factors** that affect chemotherapy **selection and dosing** are **age**, concurrent **disease states** (e.g., **Renal** failure, **heart** disease), and **performance status** (assessed through specific scales).

Combination Chemotherapy

The **principles** of using combination therapy are **to use**:

- 1) **Agents** with different pharmacologic actions
- 2) **Agents** with different organ toxicities
 - (e.g., Anthracyclines (eg, **doxorubicin**) have the potential to cause **cardiac toxicity**;
 - Microtubule-targeting agents (eg, **vincristine**) are associated with various forms of **neurotoxicity**;
 - Alkylating agents (eg, **melfhalan**) are associated with **secondary malignancies**.
- 3) **Agents** that are active against the tumor and ideally synergistic when used together
- 4) **Agents** that do not result in significant drug interactions.
- 5) **When two or more agents are used together**, the risk of development of resistance may be lessened, *but toxicity may be increased*.

Further reading :The most commonly used anticancer agents

Class	Drugs	General comment
Antimetabolites	Pyrimidine analogues like fluorouracil Purine Analogues like mercaptopurine Folate Antagonists like Methotrexate	All can cause Myelosuppression
Vinca Alkaloids	vincristine, vinblastine, and vinorelbine	Used mainly in hematological malignancies The dose-limiting toxicity of vincristine is neurotoxicity while for Vinorelbine and vinblastine is myelosuppression.
Taxanes	Paclitaxel, Docetaxel, and Cabazitaxel.	They have activity in several solid tumors. Mainly cause myelosuppression
Anthracyclines	Daunorubicin, doxorubicin, idarubicin, and epirubicin	They can cause cardiac toxicity.
Alkylating agents	Nitrogen mustard like Cyclophosphamide & ifosfamide	Cause hemorrhagic cystitis
	Nitrosoureas like carmustine and lumstine	Can cause myelosuppression and used in brain tumors
	Platinum compounds like Cisplatin, carboplatin, and oxaliplatin	Cisplatin is highly emetogenic (higher than carboplatin and oxaliplatin). There is risk of nephrotoxicity, Ototoxicity and electrolyte abnormalities.
Antibiotics	Bleomycin	Pulmonary toxicity
Monoclonal antibodies	Like almetuzumab, obintuzumab, rituximab, etc	Hypersensitivity reaction