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Advances in Cancer Chemotherapy and Pharmacology

An Overview of Cancer

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Review Article

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Abstract

Cancer is defined as one of the large groups of diseases characterized by the development of abnormal cells that grow beyond their boundaries, which can invade adjoining tissues via circulation, and spread to other organs in the body. Cancer can be initiated anywhere in the body, where damaged cells grow and multiply where they shouldn't. These cells form tumors, also called neoplasm- an abnormal mass of cells. Tumors can be non-cancerous (benign) and cancerous (malignant). Cancers are grouped according to their origin of tissue or organ.

Four major types of cancers-

- Carcinomas – are malignancies that begin in the epithelial cells, which make up the skin , and tissues that line other internal organs. Examples of carcinomas involved are prostate cancer, breast cancer, lung cancer, and colorectal cancer.
- Sarcomas- sarcoma is a type of cancer that starts in tissues like bone or soft tissues and connective tissues .
- Leukemias- leukemias are cancer of the white blood cells, which begins in the bone marrow as the bone marrow produces an excessive amount of abnormal white blood cells, that do not function properly. There are 4 major types of leukemia - acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, and chronic myelogenous leukemia .
- Lymphoma- a cancer that begins in the lymphatic system, the lymphatic system includes the lymph nodes, spleen, thymus gland, and other network of vessels. There are main types of lymphomas- Hodgkin's lymphoma and non-Hodgkin's lymphomas.
- And there are also other types of cancer
- In overview, cancer is a condition where cells multiply abnormally over time. The cells divide and grow rebelliously, they invade surrounding tissues and spread to distant parts of the body. In the course of time, the mass of the cancer cells can get massive enough to make lumps(tumors) that can be felt or seen. But not all tumors are cancer.

Keywords: Cancer; Tumor; Benign; Malignant; Carcinoma;, Sarcomas; Leukemias; Lymphoma; Acute Lymphocytic Leukemia; Chronic Lymphocytic Leukemia; Acute Myelogenous Leukemia; Chronic Myelogenous Leukemia; Hodgkin's Lymphoma; Non-Hodgkin's Lymphoma

Abbreviations: LDCT: Low Dose Computed Tomography; PFT scan: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; CT scan: Computerized Tomography; CTCs: Circulating Tumor Cells; HBV: Hepatis B Virus; HPV: Human Papillomavirus; NHL: Non-Hodgkin Lymphoma; HL: Hodgkin Lymphoma; TCC: Transitional Cell Carcinoma; BCC:

Basal Cell Carcinoma.

Introduction

A tumor can be benign or malignant, but not all tumors are malignant tumors.

- **Benign tumors**- are the abnormal growth of non-cancerous cells at a particular location and do not invade other neighboring tissues or metastasize (spread throughout the body). Benign tumors generally have slow growth rate and are relatively well-differentiated cells with distinct borders [1]. However, they enlarge and eventually compress healthy tissue either by causing pain or other medical complications such as benign tumors in the brain. Specific types of benign tumors have the potential to turn into malignant tumors, common types of benign tumors are adenomas, fibromas, osteochondroma, fibrous dysplasia, lipomas, desmoid tumors, hemangiomas, and several other types [2].
- **Malignant tumors**- Malignant neoplasm is another term for cancerous tumors, the term 'neoplasm' refers to an abnormal excessive growth of tissues. Malignancy is characterized by metastasis (a hallmark of cancer) and genome instability [3]. They also have reduced expression of DNA repair enzymes. Malignant tumors can spread rapidly and require treatment to avoid spread, not all malignant tumors grow hastily, and some may grow much slower in the course of time. There are different types of malignant tumors which include- carcinoma, sarcoma, germ cell tumor, blastoma, and meningiomas [4].

Difference between Normal Cells and Cancerous Cells

Cancer cells vary from normal cells in various ways for instance-

- Normal cells divide involving a variety of genes in controlling the growth and division of the cells with appropriate signaling, whereas cancer cells divide by themselves despite the absence of the signals and are resistant to cell apoptosis or programmed cell death [5].
- Normal cells stay in the area of their origin where they belong in the body, but cancerous cells can detach and spread via the bloodstream and lymphatic system invading other parts of the body [6].
- Normal cells mature and have a regular lifespan they either die when they get old or are damaged nevertheless, cancer cells have an irregular lifespan and grow uncontrollably [7].
- Cancerous cells fuel up their growth with different nutrients and oxygen from nearby blood vessels [8]. The central concept of tumor metabolism is described as the partial use of glucose and glycolysis for energy [9].
- Normal cells that are damaged are usually identified by the immune system and are eliminated by the immune system however, cancer cells deceive the immune system helping the cancer cells to grow and stay viable [10]. For instance, cancer cells develop genetic changes that help them to escape from the immune system.

How Does Cancer Develop?

Cancer is a genetic disorder, as it is caused by changes in the genes that control our cell function especially the way they grow and multiply. Each cell has a copy of a gene that escorts as an instruction manual [11]. Secondarily human cancer genes are considered as hereditary genes, a genetic predisposition of autosomal dominant which obtrudes a high risk for developing cancer [12].

At the cellular level, cancer development is observed as a multistage process involving mutation with cell proliferation, invasion, and metastasis [13]. Conceptually the first step is tumor initiation, tumor promotion, and tumor progression.

Tumor initiation- tumor initiation is defined as a process in which normal cells are able to transform into tumors with irreversible genetic damage [14]. Mutagens are substances that cause cancer and are considered 'tumor-initiators'. A chemical carcinogen causes a genetic error that results in gene mutation during DNA synthesis.

Tumor promotion- tumor promotion is a rate-limiting event in carcinogenesis, which promotes clonal expansion of the initiated cell and also promotes the survival of the initiated cell (ability to resist the cell apoptosis) [15]. The expression of tumor-suppressor genes is decreased which is necessary for the survival of the tumor cells. Tumor promotion is a state of cell proliferation, hyperplasia, and oxidative stress.

Tumor progression- tumor progression is the third and the last phase of tumor development, this is a complex period that is characterized by well-defined morphological and structural changes in the tumor cells which can be noticed by the rate of their growth and invasiveness of the tumor cells, that results in an increase in the malignant phenotype and becomes more aggressive overtime period [16]. Due to this conspicuous characteristic feature, the tendency for genomic instability and unrestrained growth of the tumor cells occurs and can lead to the activation of the protooncogenes and persistent functional loss of tumor suppressor genes [17].

Types of Genes Responsible for Causing Cancer

The changes in genes that affect cell growth and have the tendency to cause cancer, three main types of genes that play a major role in cancer are –

- Oncogenes
- Tumor suppressor genes

- DNA repair genes

Changes in one or any of these genes within the cell often result in the initiation of cancer [18]. Cancer cells experience various genetic alterations throughout their lifetime, but only a few of them drive cancer progression and are termed driver mutants/ drivers of cancer. Driver mutations are interconnected with clinical phenotypes and can be used as biomarkers of cancer.

Oncogenes: such as H-RAS, ErbB2, PI3KCA, MYC, and CCND1 [19].

Proto-oncogenes are the genes that are responsible for promoting normal cellular growth and cell division to produce new cells [20]. When a proto-oncogene mutates there are too many copies of cells (or) the activation of the gene, where at this point it is called **oncogenes.** In tumor cells, these genes are often expressed at high levels. Activated oncogenes get involved in processes such as cell growth, cell proliferation, and inhibition of cell apoptosis [21].

Oncogenes can be activated in different cells by–

a) Gene mutation
b) Epigenetic changes
c) Chromosomal rearrangement
d) Gene duplication

Tumor suppressor genes- such as Tp53, RB1, APC, INK4, PTEN, BRCA1 and BRCA2 .

A tumor suppressor gene is like a brake on a cycle as it prevents the cells from dividing swiftly. Oncogenes operate abnormal proliferation of the cells that increases the gene expression, whereas the tumor suppressor gene will control the cell growth, and inhibit cellular proliferation and development of the tumor [22]. A tumor suppressor gene encodes a protein that regulates cell division, for example, the Tp53 gene is an essential tumor suppressor gene found in every individual, it codes for the p53 gene which helps regulate the growth of cells [23]. When the tumor suppressor gene is mutated, it results in the loss of function in combination with other genetic mutations allowing abnormal cell growth.

DNA repair genes- they are the genes that are involved in fixing the damaged DNA if these genes fail to repair the damaged DNA they trigger the cell apoptosis process to prevent further complications [24]. If the DNA damage is not well recognized and repaired, it leads to a very critical condition resulting in cancer development and progression, these genes are involved in the recognition and removal of the defective DNA lesion and protection from errors during DNA replication [25].

Types of Cancers

There are more than 200 types of cancers and cancers are classified according to their place of origin of cancerous cells in the body (or) where cancer cell formation starts in the body, such as breast cancer occurs in the breast, brain cancer occurs in the brain, lung cancer in the lungs. Cancer is also grouped on the basis of the type of cell, for example- squamous cells or epithelial cells [26].

A few major types of cancers that begin in specific cells they are-

- **Carcinoma**- carcinomas are the most common type of cancer, these tumors form from the epithelial cells. This cancer begins in the skin or tissue that lines the internal organs. There are different types of epithelial cells where cancer initiates, which include adenocarcinoma, basal cell carcinoma (BCC), squamous cell carcinoma, and transitional cell carcinoma (TCC) [27].

a) **Adenocarcinoma**- is a type of cancer that is formed in epithelial cells that produce fluid or mucus (breast cancer, prostate cancer, lung cancer, colon cancer).
b) **Basal cell carcinoma**- basal cell cancer begins in the basal layer of the epidermis which is one individual's skin and rarely develops on mucus membranes (nodular BCC, superficial BCC, infiltrative BCC) [28].
c) **Squamous cell carcinoma**- is a cancer that forms on cutaneous squamous epithelium, which lies just beneath the outer epidermis and is also found on the lining of the throat and esophagus [29].
d) **Transitional cell carcinoma**- transitional cell carcinoma is a type of cancer that forms in transitional epithelium also called ad urothelium, this epithelium is generally found in the linings of the bladder, ureter and other parts of the urinary system (papillary TCC, non-papillary TCC [30].

- **Sarcoma**- sarcomas are cancers that form in connective tissue such as bone, cartilage, fat, muscles, blood vessels, and fibrous tissues. They are grouped into two categories-

a) **Soft tissue sarcomas**- such as malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, synovial sarcoma, dermatofibrosarcoma protuberans, angiosarcoma, Kaposi sarcoma, gastrointestinal stromal tumor, desmoid tumor.
b) **Primary bone sarcomas**- include osteosarcoma, giant cell tumor, and chondrosarcoma [31].

- **Leukemia**- leukemia is a life-threatening cancer that begins in the blood-forming tissues such as bone marrow and leads to increased production of leukocytes aggressively. These cancers do not form solid tumors. There are four subtypes of leukemia based on the rapidity of proliferation (acute or chronic) and the type of cell cancer that is initiated (lymphoblastic or myeloid) [32].
- **Lymphomas**- lymphomas are a group of cancer that is caused by the proliferation of B cells, T-cells, and NK cells. In lymphoma, an abnormal number of lymphocytes builds up in the lymphatic nodes and lymphatic blood vessels exceeding and invading into other organs of the body. There are two main types of lymphomas-

a) **Hodgkin lymphoma (HL)**- the presence of abnormal

Hodgkin Reed-Sternberg cells, these originate from B cells of the immune system [33].

b) **Non-Hodgkin lymphoma (NHL)**- a type of cancer that is formed from the lymph nodes [34].

- **Multiple myeloma**- myeloma is a cancer that begins in the plasma cells and is characterized by an abnormal increase in the number of immunoglobulins. The abnormal plasma cells called myeloma cells are built up in the bone marrow and form tumors in the bones throughout the body, excess production of these plasma cells results in end-organ damage [35].
- **Brain and spinal cord cancers**– abnormal cell growth that starts in the brain and spinal cord, as these two components together form the central nervous system. There are different types of brain and spinal cord tumors. These tumors are named based on the type of cell in which they are formed or the origin of the tumor in the central nervous system [36]. The most common type of brain tumor develops in the glial cells of the brain it is called glioma. Brain tumors are classified as-

a) **Primary tumor**- which starts in the brain.
b) **Secondary tumor/brain metastasis tumor**- they usually spread from tumors that are located outside the brain.

Signs and Symptoms

Cancer generally does not produce any symptoms, but signs and symptoms may appear as the mass grows. Cancer can be difficult to diagnose and is considered as 'great imitator'.

Multiple symptoms that are caused by cancer are-

- Abnormal Mole
- Lumps
- Chest Congestion
- Changes In Bowel Habits
- Hematuria
- Neck Lumps
- Rectal Bleeding
- Dyspnea
- Fatigue
- Weight Loss
- Hemoptysis
- Cognitive Impairment [37]

Breast changes

1) lumps or a firm feeling in the breast or surrounding areas of the breast (under the arm).
2) Changes in the nipple position
3) Nipple discharge
4) Breast pain

Bladder changes

1) Hematuria
2) Pain while urination
3) Pelvic pain

Neurological problems

1) Altered mental status
2) Headache
3) Cranial nerve palsy
4) Ataxia
5) Papilledema
6) Speech, visual loss

Skin changes

1) A new mole or changes in the existing mole
2) Pigmented papules or nodules, which may ulcerate and bleed
3) A flesh-colored lump that bleeds and turns scaly
4) Color variation [38]

Causes of Cancer

Cancer is a leading cause of death worldwide, as there is no single cause of cancer. Cancer arises from the alteration of normal cells into malignant tumors by the process of carcinogenesis/tumorigenesis. It is caused by the interaction between individual genetic factors and external factors, which are broadly classified into three (3) categories -

1) **Physical carcinogens** - such as ultraviolet, ionization, and non-ionizing radiations
2) **Chemical carcinogens** - such as arsenic (drinking water contaminant), cadmium, nickel, cobalt, asbestos, and other chemicals, components of tobacco smoke, alcohol, nanoparticles, etc.
3) **Biological carcinogens** - are living organisms that possess oncogenic viruses that have the potential to cause cancer such as; Epstein Barr virus, Human Papillomavirus (HPV), Hepatis B virus (HBV), bacterium helicobacter pylori, etc [39].

Another contribution to cause cancer is by the stimulation of cell proliferation by inducing cell mutation/ altering the genetic material, factors that cause those changes include

- Heredity
- Activation of protein kinase C
- DNA damage
- Cell division errors

How Does Cancer Spread?

Our body is made up of trillions of cells which are grouped together to form tissues and organs. Genes inside each cell regulate cell growth, cell function, cell division, and death. Generally, a normal healthy cell follows these instructions, whereas if a cell's genetic material (DNA) is damaged or mutated due to various factors, the cells that should be resting start to grow aggressively in an uncontrollable manner within a short duration resulting in the development of cancer. In adults, cells normally grow and divide according to the requirements such as the replacement of dead cells due to aging, but cancerous cells are completely divergent as

they have the ability to mutate the normal healthy cells into cancer cells (tumors) [40].

A cancer cell does not act like a normal cell, it starts to grow and continuously divide instead of cell death as gene mutations in the cancer cells interfere with the instructions of a healthy cell and prevent the cell from death. Although there are different types of cancers, it starts from any cell in the body [41].

The place where the cancer begins in the body is called primary cancer or the primary site where the cancer develops in the body. Cells break away from the primary site and spread throughout the body, and these cells grow and form tumors in other parts of the body these are called secondary cancers or metastatic cancer. Cancer cells spread to other parts of the body via blood stream and lymphatic system and they grow into new tumors [42].

Cancers are named according to their origin, and the place where they first appeared for example, colorectal cancer that has spread to the liver is called colorectal cancer with liver metastases, or bowel cancer that has spread to the lung it is called bowel cancer with lung metastases. It is because the cancerous cells in the liver and lungs are the cancerous bowel cells as they are not the liver or lung cells that have become cancerous.

As said above, the cancerous cells from the primary site should break away and then travel to other parts of the body, cancerous cells do not stick around as normal cells do, they may produce substances that stimulate them to move around [43].

Spread through the bloodstream: Cancerous cells can also enter into small blood vessels and then enter into the bloodstream, these circulating cancerous cells are called as circulating tumor cells (CTCs). then the cancer cell enters through the capillary wall and invades the tissue of the organ. In the metastases cascade there are three processes -

1) Invasion
2) Intravasation
3) Extravasation

Spread through the lymphatic system: The lymphatic system is a complex network of vessels, tissues, and organs that helps maintain fluid balance in the body by collecting excess fluid and particulate matter from the tissues and depositing them into the bloodstream. Hence, it filters body fluids and fights infection as it also traps the damaged cells and harmful cells such as cancerous cells [44].

The cancer cells enter into the nearest lymph vessel by penetrating the basement membrane that is close to the primary tumor [45]. They enter the lymphatic system and travel into the nearby lymph gland, the cancerous cells then settle and begin to proliferate and form new tumors resulting in the destruction of lymph nodes [46].

Diagnosis and Screening

Cancer mortality is reduced when cases are early detected and treated early, there are two components of early detection

a) Early diagnosis
b) Screening

Diagnosis: Diagnosing cancer in its early stages often provides the best way to cure; it because when it is identified early, cancer presumably responds to the treatment and has a higher probability of survival than morbidity. Remarkable improvements can be made in the lives of cancer patients by early detection before it causes symptoms and worsens the disease [47].

There is no single test to diagnose cancer, one or more tests to approach to diagnose cancer

- Physical examination
- Laboratory tests
- Imaging tests
- Biopsy

Physical examination: a physician may feel for the presence of lumps in the body that may indicate cancer. During the physical examination, the doctor may notice abnormalities such as skin nodules, changes in skin pigmentation, and enlargement of the mole [48].

Laboratory tests: laboratory tests such as blood tests (CBP) and urine tests (CUE) may help the doctor to find abnormalities caused by cancer. For example, in patients suffering from leukemia a complete blood picture may reveal the unusual count of different types of white blood cells.

Imaging tests: imaging tests create pictures of internal organs of the body in a non-invasive way to see whether the tumor is present. The imaging tests used in diagnosing cancer may include-

- **Computerized tomography (CT scan)**- is an imaging procedure that uses special X-ray equipment that is linked to a computer to create pictures of organs from different angles, these images are 3Dimensional images
- **Magnetic resonance imaging (MRI)**- an MRI uses powerful magnetic and radio waves to take pictures of the body in slices. These slices are combined together to create detailed images and can show the presence of tumors inside the body [49].
- **Positron emission tomography (PET scan)**- A PET scan is a type of nuclear scan that makes detailed 3D images inside the body where glucose is uptake inside the body because cancer cells often take glucose more than healthy cells. Hence, this procedure can be used to find the cancerous cells in the body after the administration of radioactive glucose [50].
- **Bone scan**- A bone scan is a type of nuclear scanning

procedure that checks for abnormal or damaged areas in the bone. They are used to diagnose bone cancers and metastatic bone tumors in the body [51].

- **Ultrasound**- ultrasound uses high-energy sound waves that people cannot hear, the sound waves penetrate off into the tissues of the body, and with the help of a computer these sound wave echoes create images of areas inside the body to detect the presence of cancer cells, this picture is called sonogram [52].
- **Nuclear medicine scan**- a nuclear medicine scan is useful especially in cancer as it shows the presence and tracks the spread of cancerous cells with the help of radioactive material injected into the body which flows through the bloodstream and gets collected in certain areas, such as organs and bones in the body .
- **X-rays**- an x-ray is a test where small doses of radiation create pictures inside the body as they can show changes in the body structure which is caused by cancer and also other medical condition [53].
- **Biopsy**- a biopsy is a procedure in which the doctor removes a sample of abnormal tissue for testing in the laboratory [54]. There are several ways through which the sample can be obtained. The right biopsy procedure depends on the type of cancer and the location of the tumor of the subject. A biopsy is the only definitive diagnostic procedure for cancer.

Screening [34]: Screening aims for the identification of specific types of cancer or pre-cancer before they have developed symptoms [55]. Screening for cancer is a form of secondary prevention from cancer, several cancer screening tests are considered effective and recommended as

- Breast cancer screening – mammography, breast MRI.
- Cervical cancer screening - human papillomavirus (HPV) tests and pap tests.
- Colorectal cancer screening - colonoscopy, stool test, sigmoidoscopy, virtual colonoscopy
- Lung cancer screening – low dose computed tomography (LDCT).
- PSA test
- Transvaginal ultrasound
- Skin examination [56,57].

Conclusion

Cancer is a multiplex of disease in which some of the body's cells grow aggressively and spread to other parts of the body due to uncontrolled cell growth and cell division by gene mutation in a normal healthy cell. Cell normally divides and increases in number by the process called mitosis. In time, the mass of cancer cells enlarges and begins to form lumps, which can be felt or seen. But not all tumors are cancerous, as tumors are broadly classified into two types benign tumors and malignant. Benign tumors are non-cancerous cells that can be removed by surgery procedures that do not invade adjacent tissues and rarely cause a threat to life. Malignant tumors are life-threatening cancerous cells that have the ability to invade and spread throughout the body via the bloodstream and lymphatic system. Metastasis is a characteristic feature of malignant tumors. Cancer can be prevented by early detection of malignant lesions. A proper plan for diagnosis and treatment is essential for the overall control of cancer, for the correct identification of the tumor, molecular diagnostic tools or microscopical evaluation (biopsy) is required. The main goal is to cure cancer patients and promise a prolonged and satisfactory quality of life. Diagnosis and treatment services should be started initially in patients suffering from curable cancers, such as cervical cancer, breast cancer, and oral cancers which are detected early. Unless the patient is suffering from acute leukemia, which has a high potential for cure but cannot be detected earlier.

Furthermore, programs should include cancer awareness, it is when people know what is cancer, and the causes of cancer. Properly educating patients, family, and community about the key risk factors and possible symptoms of cancer and their necessity for preventive measures to avoid the development of cancer.

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