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Review Article

CANCER

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INTRODUCTION

Cancer is one disease which has not been successfully managed. It affects people of all ages and can involve any part of once body.The increasing age of the population and the continuing morbidity and mortality associated with the disease confirms the need for continued scientific research and the development of new therapies.

Improved knowledge of the molecular biology of cancer and the increasing age of the general population, significant treatment options for cancer patients; all indicate the growing importance of Oncology as a science. As a result biotechnology companies continue to target cancers with unmet needs.Dabur Pharma Ltd. was having 11 plants in Mohali for manufacturing anti-cancer drugs [Plants for Taxemes—Paclitaxel & derivatives]which have been acquired by Fresenius Kabi Oncology Ltd.(German company interested in cancer research and anticancer products)

Several researchers in India are enganged in discovery & development of various new anti-cancer drugs worldwide.Before prescribing these drugs to a general public it is required to conduct clinical trials on human samples.In a recent news published in Times of India dtd.19/08/12 even the Apex court has asked government of India to conduct clinical trials of a Homeopathic drug that tends to be effective for cancer & submit the report to the Apex court within 3 weeks. The honourable judges consider Good of suffering Indian citizens.

The main purpose of this Article is to introduce the readers to general aspects of cancers. It is designed to be a review of cancer including leukemia and does not cover any specific type of cancer.

CANCER

Cancer is a affliction of the cells in the body. There are many different types of cancer which arise from different types of cell & all types of cancer have in common is that the cancer cells are abnormal and multiply out of control[1]

Origin of Cancer

All types of cancers begin within cells; the body's basic unit of life. These cells grow and divide in a controlled way to produce more cells to keep the body healthy. When cells become old or damaged, they die and are replaced with new cells[1]

Sometimes the genetic material (DNA) of a cell can become damaged or changed, producing mutations that affect normal cell growth and division. When this happens, cells do not die when they should and new cells form when the body does not need them. The extra cells may form a mass of tissue called a tumor [Benign & Malignant].The two common types for investigations of cancer include breast cancer in females& prostate cancer in males.

History

The earliest written record regarding cancer is from 3000 BC in the Egyptian Edwin Smith Papyrus and describes cancer of the breast. Hippocrates (ca. 460 BC – ca. 370 BC) described several kinds of cancer, referring to them with the Greek word carcinos (crab or crayfish)[(2)]The Greek, Celsus (ca. 25 BC – 50 AD) translated carcinos into the Latincancer, also meaning crab and recommended surgery as treatment.Galen (2nd century AD) disagreed with the use of surgery and recommended purgatives instead.The German professor Wilhelm Fabry believed that breast cancer was caused by a milk clot in a mammary duct.With the widespread use of the microscope in the 18th century, it was discovered that the 'cancer poison' spread from the primary tumor through the lymph nodes to other sites ("metastasis"). This view of the disease was first formulated by the English surgeon Campbell De Morgan between 1871 and 1874[3]

Cancer – Statistics and Epidemiology

World Health Organisation provides general information about cancer worldwide that in 2008 approximately 12.7 million cancers were diagnosed (excluding non-melanoma skin

cancers and other non-invasive cancers) and 7.6 million people died of cancer worldwide.Of these 6.6 million cases were in men and 6.0 million in women. This number is expected to increase to 21 million by 2030[4].
Cancers as a group account for approximately 13% of all deaths each year with the most common being: lung cancer (1.4 million deaths), stomach cancer (740,000 deaths), liver cancer (700,000 deaths), colorectal cancer (610,000 deaths), and breast cancer (460,000 deaths) &prostate cancer and others.This makes invasive cancer the leading cause of death in the developed world and the second leading cause of death in the developing world[5]
Global cancer rates have been increasing primarily due to an aging population and lifestyle changes in the developing world.. According to cancer researcher Robert A. Weinberg, "If human beings lives long enough, sooner or later they would be attacked by this disease" Some of the association between aging and cancer is attributed to immunosenescence,errors accumulated in DNA over a lifetime, and age-related changes in the endocrine system.
The three most common childhood cancers are leukemia (34%), brain tumors (23%), and lymphomas (12%)[6a,b,c,d,e]

Tumours[1]
As stated above atumour is a lump or growth of tissue made up from abnormal cells. There are types: benign and malignant.

Benign tumours
These may form in various parts of the body. Benign tumours grow slowly, and do not spread or invade other tissues. They are not cancerous and are not usually life-threatening. However, some benign tumours can cause problems. For example, some grow quite large and may cause local pressure symptoms, or look unsightly. Also, some benign tumours that arise from cells in hormone glands can make too much hormone, which can cause unwanted effects.

Malignant tumours (cancers)
Malignanttumours tend to grow quite quickly, and invade into nearby tissues and organs, which can cause damage. Tumours normally develop in one original site - the primary tumour. Malignant tumours may also spread to other parts of the body to form secondary tumours (metastases). This happens if some cells break off from the primary tumour and are carried in the bloodstream or lymph channels to other parts of the body & are not destroyed by the liver. These secondary tumours may then grow, invade and damage nearby tissues,andspread again.
All cancers do not form solid tumours. For example, in cancer of the blood cells (leukaemia) many abnormal blood cells are made in the bone marrow and circulate in the bloodstream.

Types
There are several types of leukemia.
It may be acute or chronic. Acute leukemia gets worsen very fast and give the sense of unwellness.compared to acute leukemia,Chronic leukemia exhibits deterioration slowly.
It may be lymphocytic or myelogenous. Lymphocytic (or lymphoblastic) leukemia affects white blood cells called lymphocytes. Myelogenous leukemia affects white blood cells called myelocytes.
The four main types of leukemia are

- Acute lymphoblastic leukemia, or ALL.
- Acute myelogenousleukemia, or AML.
- Chronic lymphocytic leukemia, or CLL.
- Chronic myelogenousleukemia, or CML.

CAUSES OF CANCER[1]
Genetic changes in cancer
Each cancer is thought to originate from one abnormal cell. Certain vital genes which control how cells divide and multiply are damaged or altered. This makes the cell abnormal. If the abnormal cell survives it may multiply out of control into a malignant tumour.

Oncogenes and tumor suppressor genes
During the 1970s,researchers discovered two particularly important families of genes related to cancer namely oncogenes and tumor suppressor genes.

Oncogenes are mutated forms of genes that cause normal cells to grow out of control and become cancer cells. They are mutations of certain normal genes of the cell called proto-oncogenes. The later are normally control how often a cell divides and the degree to which it differentiates (or specializes).
Tumor suppressor genes are normal genes that slow down cell division, repair DNA errors, and tell cells when to die (a process known as apoptosis or programmed cell death). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.
The researchers are attempted to identify the oncogenes and tumor suppressor genes that

are damaged by chemicals or radiation and those that, when inherited, can lead to cancer.

Chemical carcinogens

A carcinogen is substance (chemical, radiation, etc) that can damage a cell and make it more likely to turn into a cancerous cell.

- Tobacco smoke. Smokers are more likely to develop cancer of the lung, mouth, throat, oesophagus, bladder and pancreas.
- Workplace chemicals such as asbestos, benzene, formaldehyde and many other chemicals.

Causative Factors of cancer

Age

People of higher age are likely to develop a cancer due to an accumulation of damage to cells in the body over time. Simultaneously the body's defences against abnormal cells may become lessen in old age.

Lifestyle factors[7]

- If person eat a lot of fruits and vegetables the risk of developing certain types of cancers is reduced These foods are rich in vitamins and minerals, and also contain chemicals called antioxidants. They may protect against damaging chemicals that get into the body[8]
- Eating too much fatty food possibly increases the risk of developing certain types of cancers[9]
- The risk of developing certain types of cancers is increased by: obesity, lack of regular exercise (physical activity), and consuming a lot of alcohol[10].

Radiation

Exposure to radioactive materials and nuclear fallout can increase the risk of developing leukemia and other cancers. Too much sun exposure and sunburn (radiation from UVA and UVB) increase the risk of developing skin cancer.

Infection

Some viruses are linked to certain cancers. People with persistent infection with the hepatitis B virus or the hepatitis C virus have an increased risk of developing cancer of the liver. There is the link between the human papillomavirus (HPV) and cervical cancer[11].

Immune system

People with a poor immune system have an increased risk of developing certain cancers. For example, people with AIDS, or people on immunosuppressive therapy.

Genetic make-up

Some cancers have a strong genetic link.In certain childhood cancers the abnormal gene or genes that may trigger a cell to become abnormal and cancerous are inherited.

Hormones

Some hormones play a role in the development of cancer by promoting cell proliferation. Hormones are important agents in sex-related cancers such as cancer of the breast, endometrium, prostate, ovary, and testis, and also of thyroid cancer and bone cancer.

An individual's hormone levels are mostly determined genetically, so this may at least partly explains the presence of some cancers that run in families that do not seem to have any cancer-causing genes. For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer. These higher hormone levels may explain why these women have higher risk of breast cancer, even in the absence of a breast-cancer gene. Similarly, men of African ancestry have significantly higher levels of testosterone than men of European ancestry, and have a correspondingly much higher level of prostate cancer. Men of Asian ancestry, with the lowest levels of testosterone-activating androstanediol glucuronide, have the lowest levels of prostate cancer[12].

Non-genetic factors

Obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers. Women who take hormone replacement therapy[HRT]have a higher risk of developing cancers associated with those hormones. On the other hand, people who exercise far more than average have lower levels of these hormones, and lower risk of cancer. Osteosarcoma may be promoted by growth hormones.

PROGNOSIS

Cancer has a reputation as a deadly disease. Survival is worse in the developing world. Those who survive cancer are at increased risk of developing a second primary cancer at about twice the rate of those never diagnosed with cancer[13]

Predicting either short-term or long-term survival is difficult and depends on many factors. The most important factors are the

particular kind of cancer and the patient's age and overall health. People who are frail with many other health problems have lower survival rates than otherwise healthy people. People who report a higher quality of life tend to survive longer.[14] People with lower quality of life may be affected by major depressive disorder and other complications from cancer treatment and/or disease progression that both impairs their quality of life and reduces their quantity of life.

GENERAL DIAGNOSIS[15]

Like symptoms, the signs of cancer vary based on the type and location of the tumor. Common tests include the following:

- Biopsy of the tumor
- Blood tests (which look for chemicals such as tumor markers)
- Bone marrow biopsy (for lymphoma or leukemia)
- Chest x-ray
- Complete blood count (CBC)
- CT scan
- MRI scan
- Mammography

Most cancers are diagnosed by biopsy. Depending on the location of the tumor, the biopsy may be a simple procedure or a serious operation. Majority of the patients with cancer have CT scans to determine the exact location and size of the tumor or tumors.

A cancer diagnosis is difficult to cope with. It is important, that under these circumstances the specialist should be consulted.

SIGNS AND SYMPTOMS OF CANCER[16]

Symptoms and signs of cancer depend on the type of cancer, where it is located, and/or where the cancer cells have spread. For example, breast cancer may present as a lump in the breast or as nipple discharge while metastatic breast cancer may present with symptoms of pain (if spread to bones), extreme fatigue (lungs), or seizures (brain).

Signs and symptoms, which usually occur in most cancer patients are as follows:

- Fever (no clear infectious source, recurrent or constant)
- Fatigue (not relived by rest)
- Weight loss (without trying to lose weight)
- Pain (usually persistent)
- Skin changes (coloration, sores that do not heal, white spots in mouth or on tongue, wart changes)
- Change in bowel or bladder functions (including trouble swallowing or constipation)
- Unusual bleeding (mouth, vaginal, and bladder) or discharge
- Persistent cough or change in voice
- Lumps or tissue masses

One or more specific symptoms that are for the cancer type. For example, lung cancer may present with common symptoms of pain, but usually the pain is located in the chest. The patient may have unusual bleeding, but the bleeding usually occurs when the patient coughs. Lung cancer patients often become short of breath, and then become very fatigued.

MANAGEMENT OF CANCER PATIENTS

An important aspect in the cancer treatment is a Management of cancer patients who requires continuous counselling in addition to the treatment. They also need nutritionists,diatians,& physiatrists advice in addition to the physicians & surgeons treatment.

PATHOPHYSIOLOGY

Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell.

Cancer is fundamentally a disease of failure of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered[17].

Importance of genetics under pathophysiology

The role of genetics in cancer has already been described above. The affected genes are divided into two broad categories viz, Oncogenes &Tumor suppressor genes. Oncogenes are genes which promote cell growth and reproduction. Tumor suppressor genes are genes which inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in many genes are required to transform a normal cell into a cancer cell[18]

Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA.

Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains many copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic

material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myelogenous leukemia, and results in production of the BCR-ablfusion protein, an oncogenic tyrosine kinase.

Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, and resulting in the expression of viral oncogenes in the affected cell and its descendants.

Replication of the enormous amount of data contained within the DNA of living cells will probabilistically result in some errors (mutations).If significant error occurs, the damaged cell can "self-destruct" through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionising radiation, or hypoxia[19]

The errors which cause cancer are self-amplifying and compounding, for example:

- Mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
- Further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.
- Further mutation may cause loss of a tumour suppressor gene, disrupting the apoptosis signalling pathway and resulting in the cell becoming immortal.
- Continued mutation in signaling machinery of the cell might send error-causing signals to nearby cells.

The transformation of normal cell into cancer is akin to a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape the controls that limit normal tissue growth. This rebellion-like scenario becomes an undesirable survival of the fittest, where the driving forces of evolution work against the body's design and enforcement of order. Once cancer has begun to develop, this ongoing process, termed clonal evolution drives progression towards more invasive stages[20]

PATHOLOGY

The tissue diagnosis given by the pathologist indicates the type of cell that is proliferating, its histological grade, genetic abnormalities, and other features of the tumor. This information is useful to evaluate the prognosis of the patient and to choose the best treatment. Cytogenetics and immuno-histochemistry are other types of testing that the pathologist may perform on the tissue specimen. These tests may provide information about the molecular changes (such as mutations, fusion genes, and numerical chromosome changes) that has happened in the cancer cells, and may thus also indicate the future behavior of the cancer (prognosis) and best treatment.

CELL CULTURE AND CANCER CELL LINES

Importance of In-Vitro methods of testing new drugs

The drug discovery & development cannot start with handling of cancer patient directly without probable assertions of ADR's which might lead fatalities. An alternative to the testing is use of in-vitro methods. One of the in-vitro methods is cancer cell lines or cancer cultures.

Cell Culture[21]

Cell culture refers to the removal of cells from an animal or human or plant and their subsequent growth in a favorable artificial environment & under strict sterile conditions.The cells may be removed from the tissue directly and disaggregated by enzymatic or mechanical means before cultivation, or they may be derived from a cell line or cell strain using standard microbiological techniques.

Primary Culture

Refers to the stage of the culture after the cells are isolated from the tissue and proliferated under the appropriate conditions until they occupy all of the available substrate (i.e., reach confluence). At this stage, the cells have to be subcultured (i.e., passaged) by transferring them to a new vessel with fresh growth medium to provide more room for continued growth.

Cell Line

After the first subculture, the primary culture becomes known as a cell line or subclone. Cell lines derived from primary cultures have a

limited life span (i.e., they are finite; see below), and as they are passaged, cells with the highest growth capacity predominate, resulting in a degree of genotypic and phenotypic uniformity in the population.

Cell Strain

If a subpopulation of a cell line is positively selected from the culture by cloning or some other method, this cell line becomes a cell strain. A cell strain often acquires additional genetic changes subsequent to the initiation of the parent line.

Most cells are anchorage-dependent and must be cultured while attached to a solid or semi-solid substrate (adherent or monolayer culture), while others can be grown floating in the culture medium (suspension culture).

Cryopreservation

If a surplus of cells are available from sub-culturing, they should be treated with the appropriate protective agent (e.g., DMSO or glycerol) and stored at liquefied Nitrogen temperature,[–170°C](cryopreservation) until they are needed. For more information on sub-culturing and cryopreserving cells, refer to the Guidelines for Maintaining Cultured Cells.

Applications of Cell Culture

Cell culture is one of the major tools used in cellular and molecular biology, providing excellent model systems for studying the normal physiology and biochemistry of cells (e.g., metabolic studies, aging), the effects of drugs and toxic compounds on the cells, and mutagenesis and carcinogenesis. It is also used in drug screening and development, and large scale manufacturing of biological compounds (e.g., vaccines, therapeutic proteins). The major advantage of using cell culture for any of these applications is the consistency, reproducibility & validity of results that can be obtained from using a batch of clonal cells.

Cell lines are marketed by ---- American Type Culture Collection [ATCC], Life technologies etc.

CONCLUSION

The article includes basic overview of cancer with important aspects as role of genetics, mutations, biotechnology & other aspects. There is always a need for developing newer more effective & less toxic anti-cancer agents. The information furnished above can be usefully utilized by the drug discovery group as much as the medical profession for managing & treating the cancer patients & the relatives. The information will also be utilized by clinical pharmacist & community pharmacist.

Glossary

Cancer	Uncontrolled growth of abnormal cells in the body
Morbidity	Incidence of ill health.
Mortality	Susceptible to death
Oncology	Branch of medicine that deals with cancer.
Affliction	A state of pain, distress, or grief
Mutation	Change in a genomic sequence
Tumor	An abnormal growth of body tissue
Metastasis	The transference of disease-producing organisms or of malignant or cancerous cells to other parts of the body
Invasive	Marked by the tendency to spread
Immunosenescence	Gradual deterioration of the immune system brought on by natural age advancement.
Benign Tumor	Tumor that lacks the ability to metastasize
Malignant Tumor	Tumor that tending to become worse and end in death
Lymphocytic	Any of the nearly colorless cells found in the blood, lymph, and lymphoid tissues, constituting approximately 25 percent of white blood
Myelogenous	Produced by or originating in the bone marrow
Oncogenes	Genes that contribute to the conversion of a normal cell into a cancerous cell
Tumor suppressor genes	Gene that protects a cell from one step on the path to cancer
Immune system	System of biological structures and processes within an organism that protects against disease.
Prognosis	Medical term for predicting the likely outcome of an illness
Osteosarcoma	Type of bone cancer
Mitosis	Is the process by which a eukaryotic cell separates the chromosomes in its cell nucleus into two identical sets, in two separate nuclei.
Chromosomes	Is an organized structure of DNA and protein found in cells

Hypoxia	Diminished availability of oxygen to the body tissues.
Proliferation	The growth or production of cells by multiplication of parts
Cytogenetics	Is a branch of genetics that is concerned with the study of the structure and function of the cell, especially the chromosomes
Immunohistochemistry	Is the localization of antigens or proteins in tissue sections by the use of labeled antibodies
Cell line	A cell line is a product of immortal cells that are used for biological research.
Primary culture	A cell or tissue culture started from material taken directly from an organism, as opposed to that from an explant from an organism.
Confluence	Coming or flowing together
Cell strain	cells adapted to culture, but with finite division potential
Senescence	Is the change in the biology of an organism as it ages after its maturity.
Anchorage-dependent	A term used to characterize cells requiring a solid substratum for growth
Cryopreservation	Is a process where cells or whole tissues are preserved by cooling to low sub-zero temperatures
Cellular biology	Is a scientific discipline that studies cells
Molecular biology	Is the branch of biology that deals with the molecular basis of biological activity.
Clonal cells	Cell , cell product, or organism that is genetically identical to the unit or individual from which it was derived.

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