A Review: Comprehensive Study on Anticancer Therapy

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***Abstract*: Cancer known medically as a malignant neoplasm, is a broad group of diseases involving unregulated cell growth. Not all tumors are cancerous; benign tumors do not invade neighboring tissues and do not spread throughout the body. There are over 200 different known cancers that affect humans. Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests, or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample. Cancer is usually treated with chemotherapy, radiation therapy and surgery.**

Few symptoms are specific, with many of them also frequently occurring in individuals who have other conditions. Cancer is the new "great imitator". Cancers are primarily an environmental disease with 90–95% of cases attributed to environmental factors and 5–10% due to genetics. It is nearly impossible to prove what caused a cancer in any individual, because most cancers have multiple possible causes. Targeted therapies work by influencing the processes that control growth, division, and spread of cancer cells, as well as the signals that cause cancer cells to die naturally (the way normal cells do when they are damaged or old). One of the examples of biochemical targets produced by carcinogens is reactive oxygen species (ROS). Ionizing radiation is a complete carcinogen &produces much of its DNA damage through ROS.

***Keywords*: Cancer; Anti-cancer drug, Cancer Metastasis, Mutations, etc.**

1. INTRODUCTION

Cancer known medically as a malignant neoplasm, is a broad group of diseases involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invading nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous; benign tumors do not invade neighboring tissues and do not spread throughout the body. There are over 200 different known cancers that affect humans.[1]

The causes of cancer are diverse, complex, and only partially understood. Many things are known to increase the risk of cancer, including tobacco use, dietary factors, certain infections, exposure to radiation, lack of physical activity, obesity, and environmental pollutants. These factors can directly damage genes or combine with existing genetic faults within cells to cause cancerous mutations. Approximately 5–10% of cancers can be traced directly to inherited genetic defects. Many cancers could be prevented by not smoking, eating more vegetables, fruits and whole grains, eating less meat and refined carbohydrates, maintaining a healthy weight, exercising, minimizing sunlight exposure, and being vaccinated against some infectious diseases.[2]

Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests, or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample. Cancer is usually treated with chemotherapy, radiation therapy and surgery. The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment. While cancer can affect people of all ages, and a few types of cancer are more common in children, the risk of developing cancer generally increases with age. In 2007, cancer caused about 13% of all human deaths worldwide (7.9 million). Rates are rising as more people live to an old age and as mass lifestyle changes occur in the developing world.[3]

1.1 Definition

There is no one definition that describes all cancers. They are a large family of diseases which form a subset of neoplasms, which show some features that suggest of malignancy. A neoplasm or tumor is a group of cells that have undergone unregulated growth, and will often form a mass or lump, but may be distributed diffusely.[4]

1.2 History

Fig. No. 1: Engraving with two views of a Dutch woman who had a tumor removed from her neck in 1689.

Cancer has existed for all of human history. The earliest written record regarding cancer is from circa 1600 BC in the Egyptian Papyrus and describes cancer of the breast. Hippocrates described several kinds of cancer, referring to them with the Greek word Karakinos. This name comes from the appearance of the cut surface of a solid malignant tumor, with "the veins stretched on all sides as the animal the crab has its feet, whence it derives its name". Galen stated that "cancer of the breast is so called because of the fancied resemblance to a crab given by the lateral prolongations of the tumor and the adjacent distended veins". Celsius translated Karakinos into the Latin cancer, also meaning crab and recommended surgery as treatment. These recommendations largely stood for 1000 years. In the 15th, 16th and 17th centuries, it became acceptable for doctors to dissect bodies to discover the cause of death. The German professor Wilhelm Fabry believed that breast cancer was caused by milk clot in a mammary duct. The Dutch professor Francois de la Boe Sylvia's, a follower of Descartes, believed that all disease was the outcome of chemical processes, and that acidic lymph fluid was the cause of cancer. His contemporary Nicolaes Tulp believed that cancer was a poison that slowly spreads, and concluded that it was contagious.[5] The physician John Hill described tobacco snuff as the cause of nose cancer in 1761. This was followed by the report in 1775 by British surgeon Percival Pott that cancer of the scrotum was a common disease among chimney sweeps. 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. [6]

2. SIGNS AND SYMPTOMS

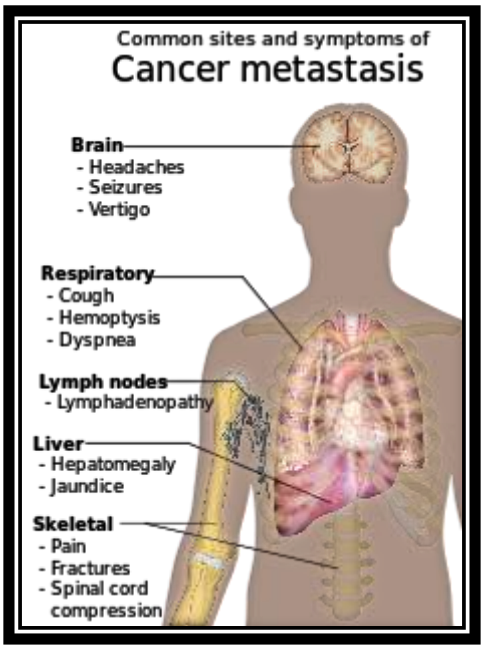


Fig. No. 2: Symptoms of cancer metastasis depend on the location of the tumor.

When cancer begins it invariably produces no symptoms with signs and symptoms only appearing as the mass continues to grow or ulcerates. [7]

2.1 Local effects

Local symptoms may occur due to the mass of the tumor or its ulceration. For example, mass effects from lung cancer can cause blockage of the bronchus resulting in cough or pneumonia; esophageal cancer can cause narrowing of the esophagus, making it difficult or painful to swallow; and colorectal cancer may lead to narrowing or blockages in the bowel, resulting in changes in bowel habits. Masses in breasts or testicles may be easily felt. Ulceration can cause bleeding which, if it occurs in the lung, will lead to coughing up blood, in the bowels to anemia or rectal bleeding, in the bladder to blood in the urine, and in the uterus to vaginal bleeding. Although localized pain may occur in advanced cancer, the initial swelling is usually painless. Some cancers can cause build up of fluid within the chest or abdomen.

2.2 Systemic symptoms

General symptoms occur due to distant effects of the cancer that are not related to direct or metastatic spread. These may include: unintentional weight loss, fever, being excessively tired, and changes to the skin. Hodgkin disease, leukemia's, and cancers of the liver or kidney can cause a persistent fever. Specific constellations of systemic symptoms, termed paraneoplastic phenomena, may occur with some cancers. Examples include the appearance of myasthenia in thymoma and clubbing in lung cancer.

2.3 Metastasis

Symptoms of metastasis are due to the spread of cancer to other locations in the body. They can include enlarged, hepatomegaly (enlarged liver) or splenomegaly (enlarged spleen) which can be felt in the abdomen, pain or fracture of affected bones, and neurological symptoms. Most cancer deaths are due to cancer that has spread from its primary site to other organs (metastasized).[8]

3. CAUSES

Cancers are primarily an environmental disease with 90–95% of cases attributed to environmental factors and 5–10% due to genetics. Environmental, as used by cancer researchers, means any cause that is not inherited genetically, not merely pollution. Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity (30–35%), infections(15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants.

3.1 Chemicals

Cancer pathogenesis is traceable back to DNA mutations that impact cell growth and metastasis. Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens. Particular substances have been linked to specific types of cancer. Tobacco smoking is associated with many forms of cancer, and causes 90% of lung cancer. Many mutagens are also carcinogens, but some carcinogens are not mutagens. Alcohol is an example of a chemical carcinogen that is not a mutagen. In Western Europe 10% of cancers in males and 3% of cancers in females are attributed to alcohol.[9]

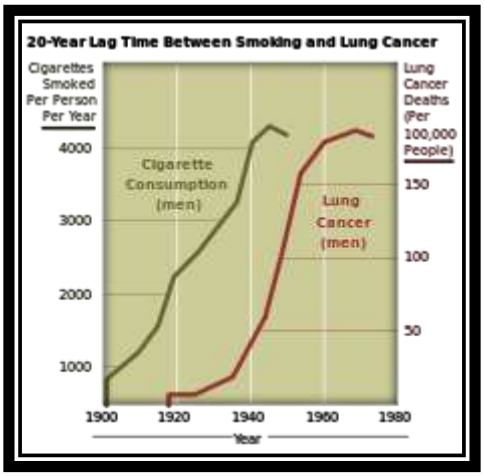


Fig. No. 3: The incidence of lung cancer is highly correlated with smoking.

3.2 Infection

Worldwide approximately 18% of cancer deaths are related to infectious diseases. This proportion varies in different regions of the world from a high of 25% in Africa to less than 10% in the developed world. Viruses are the usual infectious agents that cause cancer but bacteria and parasites may also have an effect. A virus that can cause cancer is called an oncovirus. These include human papillomavirus (cervical carcinoma), Epstein–Barr virus (B-cell lymph proliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpes virus (Kaposi's sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1(T-cell leukemia's). Bacterial infection may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma. Parasitic infections strongly associated with cancer include Schistosoma haematobium (squamous cell carcinoma of the bladder) and the liver flukes, Opisthorchis viverrini and Clonorchis sinensis (cholangiocarcinoma).[10]

3.3 Radiation

Up to 10% of invasive cancers are related to radiation exposure, including both ionizing radiation and non-ionizing ultraviolet radiation. Additionally, the vast majority of non-invasive cancers are non-melanoma skin cancers caused by non-ionizing ultraviolet radiation. Sources of ionizing radiation include medical imaging, and radon gas. Radiation can cause cancer in most parts of the body, in all animals, and at any age, although radiation-induced solid tumors usually take 10–15 years, and can take up to 40 years, to become clinically manifest, and radiation-induced leukemia's typically require 2–10 years to appear. Some people, such as those with nevoid basal cell carcinoma syndrome or retinoblastoma, are more susceptible than average to developing cancer from radiation exposure. Children and adolescents are twice as likely to develop radiation-induced leukemia as adults; radiation exposure before birth has ten times the effect. Ionizing radiation is not a particularly strong mutagen. Residential exposure to radon gas, for example, has similar cancer risks as passive smoking. Low-dose exposures, such as living near a nuclear power plant, are generally believed to have no or very little effect on cancer development. Radiation is a more potent source of cancer when it is combined with other cancer-causing agents, such as radon gas exposure plus smoking tobacco. Unlike chemical or physical triggers for cancer, ionizing radiation hits molecules within cells randomly. If it happens to strike a chromosome, it can break the chromosome, result in an abnormal number of chromosomes, inactivate one or more genes in the part of the chromosome that it hit, delete parts of the DNA sequence, cause chromosome translocations, or cause other types of chromosome abnormalities. Major damage normally

results in the cell dying, but smaller damage may leave a stable, partly functional cell that may be capable of proliferating and developing into cancer, especially if tumor suppressor genes were damaged by the radiation. Three independent stages appear to be involved in the creation of cancer with ionizing radiation: morphological changes to the cell, acquiring cellular immortality (losing normal, life-limiting cell regulatory processes), and adaptations that favor formation of a tumor. Even if the radiation particle does not strike the DNA directly, it triggers responses from cells that indirectly increase the likelihood of mutations. Medical use of ionizing radiation is a growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer.[11]

4. PATHOPHYSIOLOGY

4.1 Genetic alterations

Cancer is fundamentally a disease of tissue growth regulation failure. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered. The affected genes are divided into two broad categories. Oncogene is 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 Oncogene, the inappropriate over-expression of normal Oncogene, 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. 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.

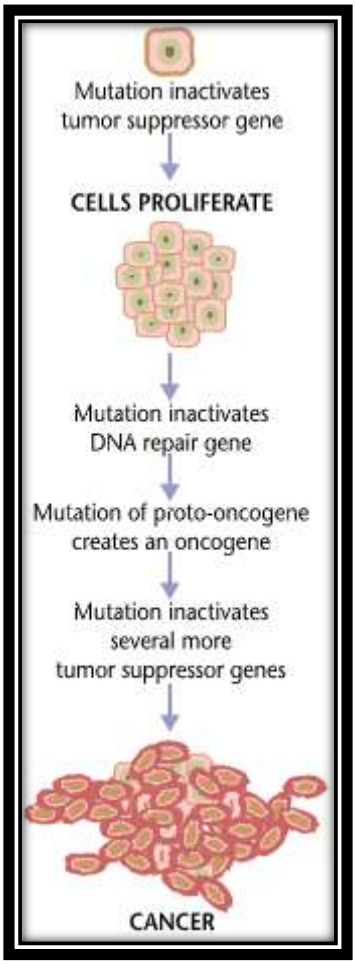


Fig. No. 4: Cancers are caused by a series of mutations.

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 oncogene 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-abl fusion protein, an oncogenic tyrosine kinase. Each mutation alters the behavior of the cell somewhat errors which cause cancer are self-amplifying and compounding, for example:

- A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
- A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.

- A further mutation may cause loss of a tumour suppressor gene, disrupting the apoptosis signaling pathway and resulting in the cell becoming immortal.
- A further 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.[12]

4.2 Epigenetic alterations

Classically, cancer has been viewed as a set of diseases that are driven by progressive genetic abnormalities that include mutations in tumour-suppressor genes and oncogenes, and chromosomal abnormalities. However, it has become apparent that cancer is also driven by epigenetic alterations.

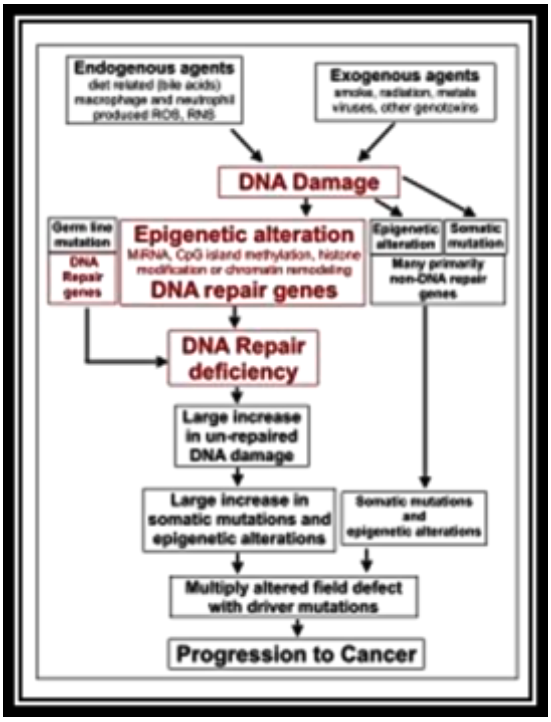


Fig. No. 5: The central role of DNA damage and epigenetic defects in DNA repair genes in carcinogenesis

Epigenetic alterations occur frequently in cancers. As an example, Schnekenburger and Diederich listed protein coding genes that were frequently altered in their methylation in association with colon cancer. These included 147 hypermethylated and 27 hypomethylated genes. Of the hypermethylated genes, 10 were hypermethylated in 100% of colon cancers, and many others were hypermethylated in more than 50% of colon cancers. The epigenetic deficiencies in expression of DNA repair genes, in particular, likely cause an increased frequency of mutations, some of which then occur in oncogene and tumor suppressor genes. [13]

5. DIAGNOSIS

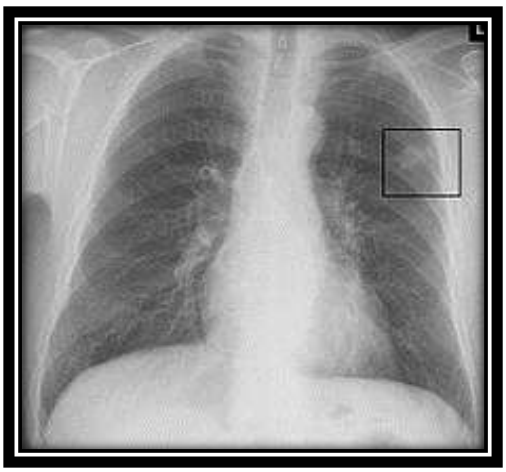


Fig. No. 6: Chest x-ray showing lung cancer in the left lung.

Most cancers are initially recognized either because of the appearance of signs or symptoms or through screening. Neither of these lead to a definitive diagnosis, which requires the examination of a tissue sample by a pathologist. People with suspected cancer are investigated with medical tests. These commonly include blood tests, X-rays, CT scans and endoscopy. Most people are distressed to learn that they have cancer. They may become extremely anxious and depressed. The risk of suicide in people with cancer is approximately double the normal risk.[14]

5.1 Classification or Type of cancer

Cancers are classified by the type of cell that the tumor cells resemble and are therefore presumed to be the origin of the tumor. These types include:

- **Carcinoma:** Cancers derived from epithelial cells. This group includes many of the most common cancers, particularly in the aged, and include nearly all those developing in the breast, prostate, lung, pancreas, and colon.
- **Sarcoma:** Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develop from cells originating in mesenchymal cells outside the bone marrow.
- **Lymphoma and leukemia:** These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively. Leukemia is the most common type of cancer in children accounting for about 30%.
- **Germ cell tumor:** Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).
- **Blastoma:** Cancers derived from immature "precursor" cells or embryonic tissue. Blastoma is more common in children than in older adults.

5.2 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. Together, this information is useful to evaluate the prognosis of the patient and to choose the best treatment. Cytogenetic and immunohisto chemistry 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.

Fig. No. 7: An invasive ductal carcinoma of the breast (pale area at the center) surrounded by spikes of whitish scar tissue and yellow fatty tissue.

Fig. No. 8: An invasive colorectal carcinoma (top center) in acolectomy specimen.

Fig. No. 9: A squamous-cell carcinoma near the bronchi in a lung specimen.

Fig. No. 10: A large invasive ductal carcinoma in amastectomy specimen. [15]

6. PREVENTION

Cancer prevention is defined as active measures to decrease the risk of cancer. The vast majority of cancer cases are due to environmental risk factors, and many, but not all, of these environmental factors are controllable lifestyle choices. Thus, cancer is considered a largely preventable disease. Greater than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, overweight / obesity, an insufficient diet, physical inactivity, alcohol, sexually transmitted infections, and air pollution. Not all environmental causes are controllable, such as naturally occurring background radiation, and other cases of cancer are caused through hereditary genetic disorders, and thus it is not possible to prevent all cases of cancer. [16]

6.1 Dietary

While many dietary recommendations have been proposed to reduce the risk of cancer, the evidence to support them is not definitive. The primary dietary factors that increase risk are obesity and alcohol consumption; with a diet low in fruits and vegetables and high in red meat being implicated but not confirmed. Consumption of coffee is associated with a reduced risk of liver cancer. Dietary recommendations for cancer prevention typically include an emphasis on vegetables, fruit, whole grains, and fish, and an avoidance of processed and red meat (beef, pork, and lamb), animal fats, and refined carbohydrates. [17]

6.2 Exercise

Diet, physical inactivity, and obesity are related to approximately 30–35% of cancer deaths. In the United States excess body weight is associated with the development of many types of cancer and is a factor in 14–20% of all cancer deaths. Physical inactivity is believed to contribute to cancer risk not only through its effect on body weight but also through negative effects on immune and endocrine system. More than half of the effect from diet is due to over nutrition rather than from eating too little healthy foods.[18]

7. Management and treatment

Many management options for cancer exist with the primary ones including surgery, chemotherapy, radiation therapy, and palliative care. Which treatments are used depends upon the type, location and grade of the cancer as well as the person's health and wishes.

7.1 Palliative care

Palliative care refers to treatment which attempts to make the patient feel better and may or may not be combined with an attempt to attack the cancer. Palliative care includes action to reduce the physical, emotional, spiritual, and psycho-social distress experienced by people with cancer. Unlike treatment that is aimed at directly killing cancer cells, the primary goal of palliative care is to improve the patient's quality of life. Patients at all stages of cancer treatment need some kind of palliative care to comfort them. In some cases, medical specialty professional organizations recommend that patients and physicians respond to cancer only with palliative care and not with cancer-directed therapy.

7.2 Surgery

Surgery is the primary method of treatment of most isolated solid cancers and may play a role in palliation and prolongation of survival. It is typically an important part of making the definitive diagnosis and staging the tumor as biopsies are usually required. In localized cancer surgery typically attempts to remove the entire mass along with, in certain cases, the lymph nodes in the area. For some types of cancer this is all that is needed to eliminate the cancer.[19]

7.3 Chemotherapy

7.3.1 What is chemotherapy?

Chemotherapy is the use of anti-cancer drugs to treat cancer. It can stop the growth of a tumor in the breast and kill cancer cells that have spread to other parts of the body. Chemotherapy may also be used to reduce the risk of breast cancer returning (recurrence), and to shrink the size of a tumor to reduce cancer-related symptoms.

7.3.2 How is it given?

Chemotherapy may be given after surgery (called adjuvant chemotherapy) or before surgery (known as neo adjuvant chemotherapy). A few anti-cancer drugs are taken by mouth or injected into the muscle or fat tissue below the skin, but most are injected into a vein. Treatments can be given at home, at the doctor’s office or in the hospital — depending on the type of chemotherapy.

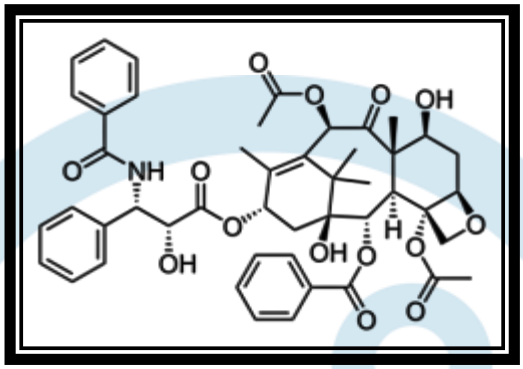
7.3.3 When is it given?

Chemotherapy usually starts within 4 to 12 weeks after surgery. It is commonly given on a 21 or 28-day cycle. Drugs are generally given weekly or once every third week, with a rest period to allow your body to recover. The length of the cycle will depend on the type of drugs used. The length of the treatment period will vary, but it often lasts from 3 to 6 months.

7.3.4 Common drugs given

In most cases, chemotherapy is most effective when combinations of drugs are given. Using different drugs together increases their ability to kill cancer cells. The drug used depends on factors such as your age, the cancer type and stage. Some drugs that are used together most often are listed below:

• Cyclophosphamide (Cytoxan)
• Doxorubicin (Adriamycin) or Epirubicin (Ellence)
• 5-fluorouracil (Adrucil)
• Methotrexate (Rheumatrex)
• Paclitaxel (Taxol) or Docetaxel (Taxotere)



Paclitaxel (Taxol)

7.3.5 Coping with side effects

Chemotherapy can also have side effects. The good news is most of these side effects are temporary. Also, the management of side effects has improved in recent years. Doctors are now using medications that can help relieve or prevent some of the side effects.

7.3.6 Common side effects

Side effects from chemotherapy depend on the drug or combination of drugs used. Side effects vary from person to person. Some of the most common side effects are described below.

a. Nausea and vomiting

Drugs called antiemetic can help reduce or prevent nausea and vomiting that can occur during chemotherapy. Eating several small meals throughout the day may also help.

b. Hair loss (alopecia)

During treatment, your hair may get thinner or may fall out entirely, depending on which chemotherapy drugs you are given. You may also have hair loss from your eyebrows, eyelashes and body. Your hair will grow back after treatment ends, but it may be a different color or texture. Using mild shampoos, soft hair brushes and low heat when drying your hair may help reduce hair loss. Some women may choose to cut their hair short beforehand to gain some control. If you would like to wear a wig, it is a good idea to get it before treatment begins so you can match your hair color and style.

c. Early menopause (when your menstrual period stops)

Some women may have menopausal symptoms such as their menstrual periods stopping, hot flashes and vaginal dryness during treatment. For women who are closer to the age of menopause (45 years or older), these symptoms may be permanent. For younger women, these symptoms may be temporary. Your doctor can help you manage these symptoms.

d. Fatigue

This is a common side effect. Try to get plenty of rest and ask family and friends to help. Exercise and a well-balanced diet may also help. Your doctor may also use a medication that may reduce fatigue.

e. Infections

Because chemotherapy reduces the white blood cell count, infections are more likely to occur. You can help prevent infections by washing your hands often and staying away from others who are ill. If you get a cut or nick, clean it right away. Your doctor should check your blood cell count before each treatment to make sure it is high enough to safely give you chemotherapy.

If you have any sign of infection such as fever while on chemotherapy, you should contact your doctor right away.

f. Mouth and throat sores

Because the cells in the mouth and throat are fast growing, some chemotherapy drugs affect these areas causing sores or dryness. Get a dental check-up before starting chemotherapy. During treatment, brush your teeth and gums after each meal and at bedtime using a soft toothbrush. Using toothpaste with baking soda and peroxide can also help. Avoid mouthwashes that contain large amounts of alcohol.

g. Weight gain

Although the reasons are unclear, some women gain weight during chemotherapy. Eating nutritious food and exercising can help maintain your normal weight.

h. Nail weakness

Some treatments can cause damage to the fingernails and toenails. The nails become brittle and sore, and may fall off. Like hair loss, nail problems are temporary.

i. Memory problems (chemo-brain)
Chemotherapy may lead to a general sense of mental fuzziness and short term memory problems. Most women say that these symptoms improve with time.

7.4 Radiation

Radiation therapy involves the use of ionizing radiation in an attempt to either cure or improve the symptoms of cancer. It is used in about half of all cases and the radiation can be from either internal sources in the form of brachytherapy or external sources. Radiation is typically used in addition to surgery and or chemotherapy but for certain types of cancer such as early head and neck cancer may be used alone. For painful bone metastasis it has been found to be effective in about 70% of people. [20]

7.5 Alternative treatments

Complementary and alternative cancer treatments are a diverse group of health care systems, practices, and products that are not part of conventional medicine. "Complementary medicine" refers to methods and substances used along with conventional medicine, while "alternative medicine" refers to compounds used instead of conventional medicine. Most complementary and alternative medicines for cancer have not been rigorously studied or tested. Some alternative treatments have been investigated and shown to be ineffective but still continue to be marketed and promoted.[20]

CONCLUSION

In conclusion, recent understanding about the unique metabolism of the solid tumor has identified several novels, drug gable pathways that may be preferentially used in tumor cells compared to normal cells. Analysis of the published reports studying Dichloroacetate shows a confusing, and sometime contradictory, range of in vitro and in vivo effects. Genetic studies in model tumors offer compelling evidence that this pathway is a good candidate for therapeutic targeting.

With the progress in molecular endocrinology of estrogens and medicinal chemistry of aromatase inhibitors, we have different strategies for inhibition of aromatase and different classes of chemical compounds to treat estrogen dependent diseases. Enhanced DNA repair, at early stage, plays a major role in cisplatin resistance.

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