ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2013; 4(5): 800 - 818

REVIEW ARTICLE

Recent Potent Molecular Targets for Cancer Treatment – A Review

Uday P. Kundap*, Rachana Sarawade

HSNCB's Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India

Received 08 Jun 2013; Revised 18 Sep 2013; Accepted 27 Sep 2013

ABSTRACT

Caner is an uncontrolled growth of cells, involving transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis & metastasis which are most important pathways for progression. Extensive research during last 30 years has revealed much about the biology of cancer. Targeted cancer therapies are the drugs or other substances that blocks the growth & spread of cancer by interfering with specific molecules involved in tumour growth & progression. By focusing on molecular & cellular changes that are specific to cancer, targeted cancer therapies may be more effective than the other types of treatment, including chemotherapy radiotherapy are less harmful to normal cells. Some of the newer molecular target therapies act by helping the immune system to destroy cancer cells. Other class includes monoclonal antibodies that deliver toxic molecules to cancer cells, cancer vaccines, Gene therapy & biological therapies for cancer. Targeted cancer therapies gives doctors a better way to tailor cancer treatment, the treatment may individualizes based on a unique set of molecular targets. Targeted cancer therapies also hold the promise of being more selective for cancer cells than normal cells, thus harming fewer normal cells, reducing side effects & improving quality of life.

Key words: Cancer, Targeted Cancer Therapy, Anti-angiogenesis, Cancer vaccine, monoclonal Antibody.

INTRODUCTION TO CANCER [1]:

We are witnessing an era of great discovery in the field of cancer research. Cancer is a major human health problem worldwide & is the second leading cause of death in the world. Over the past 30 years, significant progress has been achieved in understanding the molecular basis of cancer. The accumulation of this basic knowledge has established that cancer is a variety of distinct diseases & that defective gene causes these disease, further, gene defects are diverse in nature & can involve either loss or gain of gene function. Cancer is a condition caused by uncontrolled growth of cells. Different kinds of cancer are named according to the type of cells that is growing in an uncontrolled way. Cancer can arise from nearly any part of the body.

Normally life processes are characterized by the continuous growth & maturation of cells, & all cells are subjected to controlled mechanisms that regulate their growth rate.This on-going growth process serves the purpose of replacing cells that have been injured or have undergone degenerative changes. Normal cells grow, divide & eventually die. In control, a neoplasm (neo = new + plasma = growth) is an overgrowth of cells that serves no useful purpose. Cancer occurs when cell growth continues unchecked, cancer cells continue to grow & divide & eventually overrun the healthy cells. Tumor that cannot invade neighbouring tissues or spread to other parts of the body are called benign tumor, on other hand when cancer cells enters the bloodstream or the lymphatic

*Corresponding Author: Uday P. Kundap, Email: uday.kundap@yahoo.com, Phone No: +91-9820603169

system they have the potential to travel to other part of the body & take over the tissues in other organs or spread of cancer cells from one part of the body to another distant site is called metastasis. The ability- and proclivity- of cancer cell to crowd out healthy cells is why the disease is so deadly.

Causes of cancer:

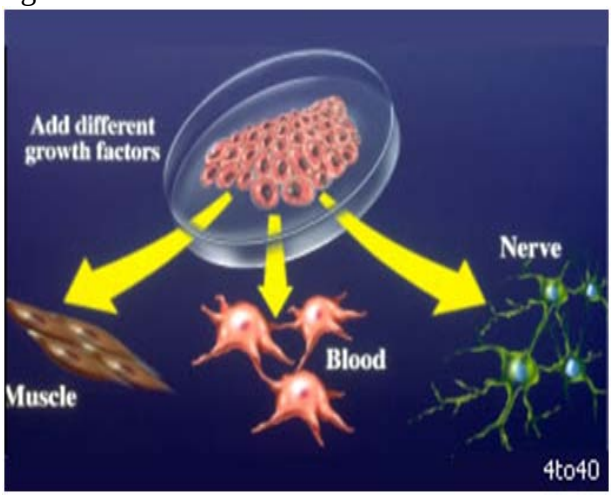
From the earliest times, physicians have puzzled over the causes of cancer. Ancient Egyptians blamed cancer on the god. The cause of cancer is usually a mutation to the genetic information (DNA) of the cell. These mutation can be due to many causes, with certain cancer causing chemicals (carcinogens), radiation (UV rays in sunlight's), & viruses like (The human papillomavirus) acting as possible triggers.

Oncogenes & tumor suppressor genes**:** - Oncogenes are mutated forms of genes that cause normal cells to grow out of control & become cancer cells. They are mutations of certain normal gene of the cell called proto-oncogenes that normally control how often a cell divides & degree to which it differentiates. Tumor suppressor genes are normal gene that slows down cell division, repairs DNA errors, & tell cells when to die (a process 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.

All the cancer cells shares the same fundamental characteristics of uncontrolled growth & ability to invade neighbouring tissues and/or spread to distant sites. The transformation of normal cells into cancer cells is the result of genetic damage. Environmental chemicals, radiations, & a person's genetic makeup can all contribute to the genetic damage that leads to the development of cancer. Tumor suppressor genes & oncogenes are the two major categories of genes involved in development of cancer.

What is cell Differentiation? [1]

When a cell grows and develops normally, it undergoes a maturation process in which it becomes specialized to perform specific function. This maturation process is called cell differentiation. Differentiation causes cells to take specific characteristics that reflect the function of the tissue the cell came from through cell division. Therefore, a new, differentiated lung cell looks & function like all other lung cells. As cell becomes more differentiated, they become more restricted in what they can do. Differentiation is the reason a kidney cell cannot behave as a muscle cell, & a lung cell cannot function as a brain cell.

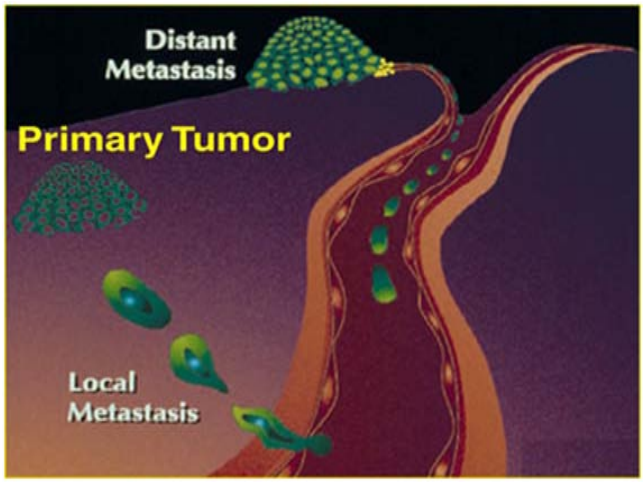


Abnormal cell proliferation can begin at any point during a cell's differentiation process. When a single cell divides, it results in two daughter cells. The daughter cells typically have the same cellular characteristics of their parent cell. If an immature or undifferentiated cell begins proliferating, all the cells produced from the original cell will also be undifferentiated. Differentiation is a process. Therefore, cells that begin proliferating abnormally can reflect varying degrees of differentiation.

The term differentiation is also used to describe how the cell of a tumor appear compared to normal cells from the tissue in which the tumor arose. Tumor classified as well differentiated contain cells that bear some degree of resemblance to the normal cells of the original tissue. Undifferentiated tumor has cells that no longer look like normal cells.

How does cancer spread? [1]

One of the defining characteristics of cancer cells is their ability to invade neighbouring tissues & to metastasize or spread to site of the body distant from the tissue of origin. Metastasis occurs when cancer cells break away from the original tumour. The cells travel through the body via the blood or lymphatic system to another part of the body where they grow & proliferate forming a new tumor. Cancer are named accordingly to the tissue from which they originated. When cancer cells metastasize and new tumour grows in different tissues, it is still the same cancer. Therefore, someone with lung cancer may have tumour in several different places, but the entire tumour is the results of the lungs cancer, which has metastasized to other location.



TRADITIONAL TREATMENT FOR CANCER:

1. Surgery
2. Chemotherapy
3. Radiation therapy
4. Hyperthermia
5. Photodynamic therapy
6. Laser in cancer treatment.

SUMMARY:

All the cancer cells share the same fundamental characteristics of uncontrolled growth & ability to invade neighbouring tissues and/or spread to distant site. The transformation of normal cells into cancer cells is the result of genetic damage. Environmental chemicals & a person's genetic makeup can all contribute to the genetic damage that leads to the development of cancer. Tumor suppressor genes & oncogenes are the two major categories of genes involved in development of cancer.

Approximately 9 million individuals alive today have been diagnosed with cancer at some point in their lives. Cancer is the second leading cause of death in the world. Currently, one out of every four individuals dies in cancer.

TARGETED CANCER THERAPIES: [2,5]

The first description of cancer is found in an Egyptians papyrus & dates back to approximately 1600 BC. It was regarded as an incurable disease until the 19th century, when surgical removal was made more efficient by anaesthesia, improved techniques & histological control. Before 1950, surgery was most preferred means of treatment. After 1960, radiation therapy started being used to control local diseases. However, over time it was realized that neither surgery nor radiation or the two in combination could adequately control the metastasis cancer & that, for treatment to be effective, therapy needed to reach every organ of the body. Therefore, current efforts to cure cancer have been focusing on drug, biological molecules & immune mediated therapies. The introduction of nitrogen mustard in the 1940s can be considered the origin of anti-neoplastic chemotherapy targeting all tumor cells. To date, cancer remains one of the most lives threatening disease. Efforts to fight this disease were intensified when the US passed the national cancer ACT in 1971 &President Nixon declared a "war on Cancer". Today, more than 30yrs later, although we have not improved mortality rate or prolonged survival time for metastatic cancer as much as we would had expected, we have identified the characteristics & pathway of different tumor entities. This knowledge is now used to generate specific tumor therapy either by directly targeting the proteins involved in the neoplastic process or by targeting drugs to the tumor. Targeted therapy encompasses a wide variety of direct & indirect approaches. Direct approaches target tumor antigens to alter their signalling either by monoclonal antibodies (MoAbs2) or by small molecule drugs that interfere with these targets proteins. Indirect approaches rely on tumor antigens expresses on the cell surface that serves as target devices for ligands containing different kinds of effector molecules. In this approach, drugs can actively target tumor using tumor-specific MoAbs2 or peptides ligands binding to receptors that are present on tumor cells.

Overview of targeted Cancer therapy: [5]

Targeted cancer therapies are drugs or other substances that blocks the growth and spread of cancer by interfering with specific molecules involved in tumor growth & progression. Because scientists often call these molecules "molecular targets", targeted cancer therapies are sometimes called as "molecular targeted drugs", "molecular targeted therapies". By focusing on molecular & cellular changes that are specific to cancer, targeted cancer therapies may be more effective than other types of treatment, including chemotherapy & radiotherapy and less harmful to normal cells.

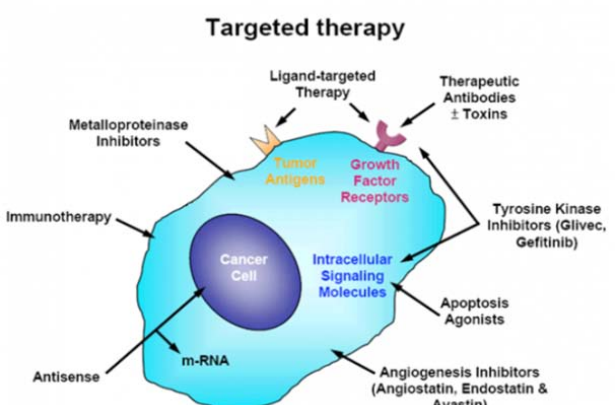
Many targeted cancer therapies have been approved by the U.S. Food & Drug Administration (US-FDA) for the treatment of specific types of cancer. Other are being studies in clinical trials (research study with peoples), and many more are in preclinical testing's (research studies with animals). Targeted cancer therapies that have been approved for use in specific cancer include drugs that interfere with cell growth signalling or tumor blood vessel development,

promote the specific death of cancer cells, stimulating the immune system to destroy specific cancer cells, and deliver toxic drugs to cancer cells. Targeted cancer therapies are being studies for use alone, in combination with other targeted therapies, & in combination with other cancer treatment, such as chemotherapy.

Working of targeted cancer therapy: [5]

Targeted cancer therapies interferes with cancer cell divisions (proliferation) & spread in different ways. Many of these therapies focus on proteins that are involved in cell signalling pathways, which form a complex communication system that governs basic cellular functions & activities, such as cell divisions, cell movements, cell responses to specific external stimuli, and even cell death. By blocking signals that tell cancer cells to grow & divide uncontrollably, targeted cancer therapies can help to stop cancer progression & may induce cancer cell death through a process known as apoptosis. Other targeted therapies can cause cancer cell death directly, by specifically inducing apoptosis, or indirectly, by stimulating the immune system to recognize and destroy cancer cells and/or by delivering toxic substances directly to the cancer cells.

The development of targeted therapies, therefore, requires the identification of good targets that is, targets that are known to play a key role in cancer cell growth & survival. (It is for this reason that targeted therapies are often referred to as the product of **"rational drug design.")** For example, most cases of chronic myeloid leukaemia (CML) are caused by the formation of a gene called BCR-ABL. This gene is formed when piece of chromosome 9 & chromosome 22 break off and trade place. One of the changed chromosomes resulting from this switch contains part of the ABL gene from chromosome 9 fused to part of the BCR gene. The protein normally produced by the BL gene (Abl) is a signalling molecule that plays an important role in controlling cell proliferation as usually must interact with other signalling molecule to be active. However Abl signalling is always active in the protein (Bcr-Abl) produced by the BCR_ABL fusion gene. This actively promotes the continuous proliferation of CML cells. Therefore, Bcr-Abl represents a good molecule to target.



Development of targeted cancer therapy: [2,5]

Once a target has been identifies, a therapy must be developed. Most targeted therapies are either small-molecule drugs or monoclonal antibodies. Small-molecule drug are typically able to diffuse into cells & can act on targets are found inside the cell. Most monoclonal antibodies cannot penetrate the cell's plasma membrane & are directed against targets that are outside cells or on the cell surface.

Impact of targeted therapy on treatment of cancer: [5]

Targeted cancer therapies give doctors a better way to tailor cancer treatment, especially when a target is present in some but not all tumor of a particular type. Eventually, treatment may be individualizes based on the unique set of molecular targets produced by the patients tumor. Targeted cancer therapies also holds the promise of being more selective for cancer cells than normal cells, thus harming fewer normal cells, reducing side effects, and improving quality of life. Nevertheless, targeted therapies have some limitations. Chief among these is the potential for cell to develop resistance to them. In some patients who have developed resistance to imatinib, for example, a mutation in the BCR-ABL gene has arisen that changes the shape of the protein so that it no longer binds this drug as well. In most cases, another targeted therapy that could overcome this resistance is not available. It is for this reason that targeted therapies may work best in combination, either with other targeted therapies or with more traditional therapies.

Targeted therapy refers to a new generation of cancer drugs designed to interfere with a specific target protein that is believed to have a critical

role in tumor growth or progression. The molecular identification of cancer antigens has opened new possibilities for the development of effective immunotherapies, antibodies therapy & ligand- targeted therapy for cancer patients.

MOLECULAR TARGETES FOR CANCER TREATMENT:[3]

- **First target for targeted cancer therapy.**
  - **Cellular receptor-**
    a) Estrogen receptor (ER)
    b) Aromatase inhibitors (AI's)
  - **Newer molecular targets.**
    a. Anti-angiogenesis-targeted therapy that blocks the growth of blood vessels
    b. Some targeted therapies act by helping the immune system to destroy cancer cells.
    c. Apoptosis- targeted therapy that undergoes cell death.
    d. Gene expression-therapy that modify the function of protein that regulates gene expression.
  - **Future consideration: Biological therapies**
    a) Monomolecular antibodies – Targeted therapies include monoclonal antibodies that deliver toxic molecules to cancer cells specifically.
    b) Cancer vaccines – contain information on vaccines intended to treat cancer.
    c) Gene therapy - Gene therapy for cancer discusses research with genetic material in development cancer therapies, including risks, benefits & ethical issues.

MOLECULAR TARGETS FOR CANCER TREATMENT: [3]

- **First target for targeted cancer therapy.**
  - **Cellular receptor-**
    1. Estrogen receptor (ER)
    2. Aromatase inhibitors (AI's)

Oestrogen receptor (ER):

The first molecular target for targeted cancer therapy was the cellular receptor for female sex hormone oestrogen, which many breast cancers required for growth. When oestrogen binds to the estrogen receptor (ER) inside the cell, the resulting hormones-receptor complex activates the expression of specific genes, including genes involved in cell growth and proliferation. Research has shown that interfering with oestrogen's ability to stimulate the growth of breast cancer cells that have these receptors (ER-positive breast cancer cells) is an effective treatment approach.Several drugs that interfere with estrogen binding to the ER have been approved by FDA for the treatment of ER positive breast cancer. Drugs called selective estrogen receptor modulators (SERMs), including tamoxifen and toremifene(fareston), bind to the ER and prevent estrogen binding. Another drug, fulvestrant (Faslodex), binds to the ER and promotes its destruction, thereby reducing ER levels inside cells.

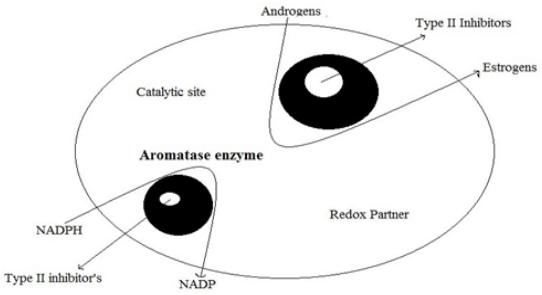
Aromatase Inhibitors (AI's):

Aromatase inhibitors (AIs) are another class of targeted drugs that interfere with oestrogen's ability to promote the growth of ER positive breast cancers. The enzyme aromatase is necessary to produce estrogen in the body. Blocking the activity of aromatase lowers estrogen levels and inhibits the growth of cancers that need estrogen to grow. AI's are used mostly in women who have reached menopause because the ovaries of premenopausal women can produce enough aromatase to override the inhibition. Three AI's have been approved by FDA for treatment of ER positive breast cancer: Anoatrozole (Arimidex) ,Exemestane (Aromanis) and Letrozole (fermare)

Mechanism of action:

There are two types of AI's,**irreversible steroidal activators and reversible non-steroidal imidazole based inhibitors.** Although both types interfere with the final step in oestrogen biosynthesis, they do so by different mechanism. Steroidal agents such as exemestane have an androgen structure and compete with the natural aromatase substrate, androstenedione, they bind irreversibly by covalently bonding to the catalytic site of aromatase causing the loss of enzymatic activity and more aromatase enzyme must be produced before oestrogen biosynthesis can resume. Therefore steroidal agents are often referred as **suicidal inhibitors**. Because of their steroidal nature exemestane and 17 hydroexemestane have potential for androgenic effects.

Permanent inactivation persists after discontinuation of drugs until the peripheral tissues synthesize new enzyme.



Non-Steroidal imidazole based agents reversibly interact with cytochrome P450 moiety of the enzyme and interference with oestrogen biosynthesis is dependent on continued presence of non-steroidal agents, Non-steroidal agents includes second generation agent aminoglutethimide& third generation agent, anastrozole and Letrozole. Third generation AIs (ieanastrozole, letrozole and exemestane) are the most potent, most selective and least toxic AIs known today and can reduce serum oestrogen by more than 95% .

NEWER MOLECULAR TARGETS:

FDA approved targeted therapies are listed below: [10]

1. Some targeted therapies block the growth of blood vessels to tumor **(Angiogenesis).**
2. Some targeted therapies act by helping the **immune system** to destroy cancer cells.
3. Some targeted therapies induce cancer cells to undergo **apoptosis** (Cell death)
4. Targeted therapies modify the function of proteins that regulate gene expression & other cellular functions.
5. Targeted therapies that block specific enzymes & growth factor receptor involved in cancer cell proliferation, these drugs are also called signal transduction inhibitors.

Anti-angiogenesis

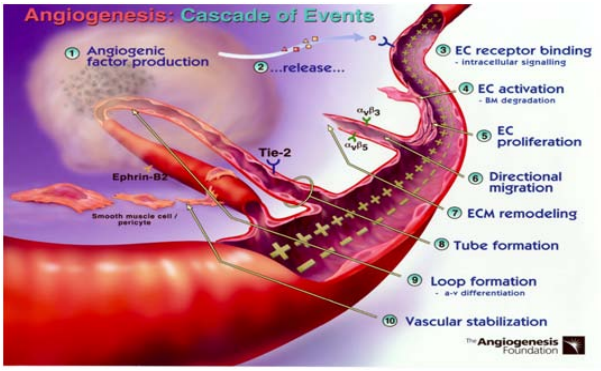
Targeted therapy that blocks the growth of blood vessels.

Angiogenesis is the formation of new blood vessels. Angiogenesis plays an important role in the growth & spread of cancer. New blood vessels feed the cancer cells with oxygen & nutrients, allowing these cells to grow, invade nearby tissues, spread to other parts of the body, and forms new colonies of cancer cells.

Angiogenesis is the process of making new blood vessels. The term comes from 2 Greek words: “angio, meaning blood vessel, and genesis, meaning beginning”. In most cases, this is a normal, healthy process. As the human body grows and develops, it needs to make new blood vessels to get blood to all of its cells. As adults, we don't havequite the same need for making new blood vessels, but there are times when angiogenesisis still important. New blood vessels, for instance, help the body heal wounds and repair damage. But in a person with cancer, this same process creates new, very small blood vessels that give a tumor its own blood supply and allow it to grow. Anti-angiogenesis is a form of targeted therapy that uses drugs or other substances to stop tumor from making new blood vessels. Without a blood supply, tumor can't grow.

Angiogenesis plays a critical role in the growth and spread of cancer. A blood supply is necessary for tumor to grow beyond a few millimetres in size. Tumor can cause this blood supply to form by giving off chemical signals that stimulate angiogenesis. Tumor can also stimulate nearby normal cells to produce angiogenesis signalling molecules. The resulting new blood vessels “feed” growing tumor with oxygen and nutrients, allowing the cancer cells to invade nearby tissue, to move throughout the body, and to form new colonies of cancer cells, called metastases.

Because tumor cannot grow beyond a certain size or spread without a blood supply, scientists are trying to find ways to block tumor angiogenesis. They are studying natural and synthetic angiogenesis inhibitors, also called anti-angiogenic agents, with the idea that these molecules will prevent or slow the growth of cancer.



The process of angiogenesis occurs as an orderly series of events:

1. Diseased or injured tissues produce and release angiogenesis growth factor (proteins) that diffuse into the nearby tissues.

2. The angiogenesis growth factor binds to specific receptors located on the endothelial cells (EC) of nearby pre-existing blood vessels.
3. Once growth factor bind to their receptor, the endothelial cells becomes activated, signals are sent from the cell's surface to the nucleus.
4. The endothelial cell's machinery begins to produce new molecules including enzymes. These enzymes dissolve tiny holes in the sheath-like covering (basement membrane) surrounding all existing blood vessels.
5. The endothelial cells begins to divide (proliferates) and migrates out through the dissolved holes of the existing vessel towards the diseased tissues (tumor).
6. Specialized molecules called adhesion molecules called integrin's (avb3, avb5) serves as grappling hooks to help pull the sprouting new blood vessel sprout forward.
7. Additional enzymes (matrix metalloproteinase or MMP) are produced to dissolve the tissue in front of the sprouting vessels tip in order to accommodate it. As the vessels extends, the tissue is removed around the vessels.
8. Sprouting endothelial cells roll up to form a blood vessel tube.
9. Individual blood vessel tubes connect to form blood vessel loops that can circulate blood.
10. Finally, new formed blood vessels tubes are stabilized by specialized muscle cells (smooth muscle cells, peri-cyte) that provide structural support. Blood flow then begins.

How can angiogenesis be stopped in tumor? [10]

Anti-angiogenesis therapies work to stop the development of new blood vessels and destroy existing abnormal vessels surrounding tumor. The goal is to cut off the fuel supply to growing tumor, causing tumor cells death. Because tumor cannot grow or spread without the formation of new blood vessels, scientists are trying to find ways to stop angiogenesis. They are studying natural and synthetic angiogenesis inhibitors, also called anti-angiogenic agent, in the hope that these chemicals will prevent or slow down the growth of cancer by blocking the formation of new blood vessels.

Researchers are investigating a number of ways to stop or alter the angiogenesis process, including: -

1. Blocking initial signals from the tumor.
2. Making initial signals from the tumor less effective.
3. Stopping the enzyme pathway.
4. Preventing the switch from turning on.

How anti-angiogenesis drugs work: [10]

Anti-angiogenesis drugs don't attack cancer cells directly. Instead, they target the blood vessels the cancer cells need to survive and grow. By doing this, they may help prevent new tumor from growing. They may also make large tumor shrink if their blood supply is cut off. Scientists have found a number of different pathways that cancer cells can use to cause blood vessel growth. Each step in these pathways is a possible target for cancer treatment. Different drugs may work at different steps in these pathways.Angiogenesis requires the binding of signalling molecules, such as vascular endothelial growth factor (VEGF), to receptors on the surface of normal endothelial cells. When VEGF and other endothelial growth factors bind to their receptors on endothelial cells, signals within these cells are initiated that promote the growth and survival of new blood vessels.For example, one of the most important proteins in new blood vessel growth is vascular endothelial growth factor (VEGF). This protein is not made in large amounts by normal cells, but some cancer cells make it and release it into the area around them. VEGF then attaches to a protein (called the VEGF receptor, or VEGFR) on the surface of nearby endothelial cells. This signals the cells' control centres, to start growing and forming new blood vessels. Many of the anti-angiogenesis drugs used today attack the VEGF pathway. Bevacizumab (Avastin®) was the first drug targeted at new blood vessels to be approved for use against cancer. It is a monoclonal antibody -- a man-made version of an immune system protein - - that binds to VEGF and keeps it from reaching the VEGF receptor. Other drugs, like sunitinib (Sutent®) and sorafenib (Nexavar®), are small molecules that attach to the VEGF receptor itself, keeping it from being turned on and making new blood vessels.

Drugs that target other blood vessel pathways are now being tested. Some drugs already used to treat cancer have been found to affect blood vessel growth, too. But it's not clear how they work. For example, doctors have found that some chemotherapy drugs, if given around the clock in low doses, may prevent tumor growth without causing the serious side effects that higher doses would. Some research suggests the drugs may work because they stop the growth of endothelial cells. Some other drugs used to treat cancer, such as thalidomide (Thalomid®) and lenalidomide(Revlimid®), are also known to affect blood vessel growth. But they work against cancer in other ways, too.

How anti-angiogenesis drugs affect tumor: [10]

Because chemotherapy and anti-angiogenesis drugs don't affect the same parts of the body, they can sometimes be given together. When chemotherapy drugs work, they often cause tumorto shrink a lot, sometimes even making them disappear. But anti-angiogenesis drugs don't seem to work in the same way. In some cases they shrink tumor, but in others they just seem to stop them from growing any larger. (This is probably because the tumor has already grown some blood vessels.) Although this may help some people, it's not yet clear how long patients need to keep taking these drugs to keep the tumor from growing. Some patients may need long-term or maybe even life-long treatment. Newer approaches that combine anti-angiogenesis drugs with chemotherapy, other targeted drugs, or radiation may work better than using them alone. For instance, early studies that tested the drug bevacizumab (Avastin) by itself did not find that it helped people with cancer to live longer. But later studies found that when it was used along with chemotherapy to treat certain cancers, it helped people live longer than if they got the chemotherapy alone. Doctors aren't sure why this is the case. One theory is based on the fact that chemotherapy drugs may have a hard time getting to cells in the middle of tumor. Tumor blood vessels grow in a short amount of time and in an abnormal environment, so they are not as well-made and as stable as normal blood vessels. Because of this, they tend to be leaky. This affects how well drugs can reach the inside of the tumor. The theory is that bevacizumab may somehow stabilize these tumor blood vessels for a short period of time, allowing the chemotherapy to reach more tumor cells and be more effective. Research in this area is ongoing.

Chemotherapy drugs can be useful in treating many types of cancer, but some cancers do not respond well to them. In some cases, anti-angiogenesis drugs may prove to be a better option. For example, chemotherapy isn't helpful against kidney cancer. But doctors have long known that kidney tumor tend to form many blood vessels. Anti-angiogenesis drugs, such as sunitinib (Sutent) and sorafenib (Nexavar), have been shown to be useful against this type of cancer. Many doctors now consider these drugs to be the best treatments when systemic therapy is needed. Because of the way anti-angiogenesis drugs work, they are only useful in treating cancers that form tumor. They won't work against blood cancers like leukemias.

How are angiogenesis inhibitors different from conventional anticancer drugs?

Angiogenesis inhibitors are unique cancer-fighting agents because they tend to inhibit the growth of blood vessels rather than tumor cells. In some cancers, angiogenesis inhibitors are most effective when combined with additional therapies, especially chemotherapy. It has been hypothesized that these drugs help normalize the blood vessels that supply the tumor, facilitating the delivery of other anticancer agents, but this possibility is still being investigated. Angiogenesis inhibitor therapy does not necessarily kill tumor but instead may prevent tumor from growing. Therefore, this type of therapy may need to be administered over a long period.

Drugs approved by FDA: [11,12]

1. **Bevacizumab (Avastin)**
   It is a monoclonal antibody that is approved for the treatment of glioblastoma. The therapy is also approved for some patients with non-small cell lungs cancer, metastatic colorectal cancer, & metastatic kidney cancer. Avastin binds to VEGF & prevents it from interacting with receptors on endothelial cells, blocking a step that is necessary for the initation of new blood vessel growth.
2. **Sorafenib (Nexavar)**
   It is a small-molecule inhibitor of tyrosine kinase that is approved for the treatment of advanced renal cell carcinoma & some cases of hepatocellular carcinoma. One of the kinase that sorafenib inhibits is involved in the signalling pathway that is initiated when VEGF binds to its receptor. As a result, new blood vessels development is halted. It also blocks an enzyme that is involved in cell growth & division.
3. **Sunitinib (sutent)**
   It is another small-molecule tyrosine kinase inhibitor that is approved for the treatment of patients with metastatic renal cell carcinoma, gastrointestinal stromal tumor that is not responding to imatinib, or pancreatic neuroendocrine tumors that cannot be removed by surgery, are locally advanced, or have metastasized. It blocks kinase involved in VEGF signalling, thereby inhibiting angiogenesis & cell proliferation.
4. **Pazopanib (votrient)**

It is approved for the treatment of patients with advanced renal cell carcinoma. Pazopanib is a small-molecule inhibitor of several tyrosine kinases, including VEGF receptor, c-kit, & platelet-derived growth factor receptor.

Immunotherapy: [3, 4]

Immunotherapy is treatment that uses your immune system to fight cancer. The 2 main ways that this is done is to boost the patients won immune system or to give man made versions of the normal parts of the immune system. Many future advances against cancer will probably come from this field.

What is Immunotherapy?

Immunotherapy is form of biologic therapy or biotherapy. It is treatment that uses certain parts of the immune system to fight disease, including cancer. This can be done in couple of ways:

- Stimulating your own immune system to work harder or smarter.
- Giving you immune system components, such asmanmade immune system proteins Immunotherapy is sometimes used by itself to treat cancer, but it is most often used along with or after another type of treatment to boost its effects.

For a long time doctors suspected that the immune system has an effect on certain cancers. Even before the immune system was well understood, William Coley MD a New York surgeon, First noted that getting infection after surgery seemed to help some cancer patients. In the late 1800s he began treating cancer patients by infecting them with certain kinds of bacteria, which came to be known as coley toxins. Although he had some success, his technique was overshadowed when other forms of cancer treatment, such as radiation therapy, came into use. Doctors have learned a great deal about the immune system since then. This has led to research into how it can be used to combat cancer and exploring many different approaches. In the last few decades immunotherapy has proven useful in treating several type of cancer. The idea of using one's own immune system to fight cancer is tempting, but so far, in most cases immunotherapy hasn't been shown to clearly be better than other forms of treatment. For instant, it seems to work best when treating smaller, early stage cancer, and it may be less helpful for more advance disease. Its main role at this time is making other forma of treatment better, or giving cancer patients a treatment option in the field. Never treatment are now being tested that seen to work better and will have greater impact on the outlook for people with cancer in future.

- **Role of Immune System**

The Immune System is your body's defence force. It helps keep invading germs out, or helps kills them if they do get into your body. Your immune system is a collection of organs, special cells, and substance that help protect you from some infections and disease. Immune system cells and the substances they make circulate through your body to protect in from germs that cause infections. They also help protect you from cancer in some ways. It helps to think of your body as a castle. Think of viruses, bacteria and parasites as hostile, foreign armies that are not normally found in your body. They try to invade your body to use its resources to serve their own purposes, and they can hurt you in the process. In fact, doctors often use the word foreign to describe invading germs or other substances not normally present in the body.

- **The Immune Response**

Any substance that raises an alarm in the body, causing the immune system to react to and attack it is called as antigen. This immune response can lead to destruction of both the antigens and anything they are attached to, such as germs or cancer cells. Germs such as viruses, bacteria and parasites have substances on their outer surfaces, such as certain proteins, that are not normally found in the human body. The immune system sees these foreign substances as antigens. Cancer cells are also different from normal cells in the body. They often have unusual substances on their outer surfaces that can act as antigens. But the immune system is much better at recognizing and attacking germs than cancer cells. Germs are very different from normal human cells and are seen as truly foreign, but cancer cells and normal cells can be very much alike, with fewer clear cut differences. Because of this the immune system may not always recognize cancer cells as foreign. Cancer cells are less like soldiers of an invading army and more like traitors within the ranks of the human cell population. This may be why cancers are often able to grow in spite of healthy, working immune system.

- **Players of Immune System**

Your immune system responds to antigens in highly coordinatedprocess that uses many types of cells. Most cells of the immune system are lymphocytes, a type of white blood cells. Several types of lymphocytes work together to attack cancer cells:

- B cells(B lymphocytes)
- T Cells(T Lymphocytes) : killer T cells, helper T Cells, regulatory (suppressor) T cells
- Natural killer (NK) cells.

Antigen- presenting cells (APCs) are not lymphocytes but work closely with them to fight cancer. They take part of the foreign cell and carry it to where other immune cells can "see" it. This helps stimulate the immune reaction. The 2main groups of antigen presenting cells are:

- Monocytes and macrophages
- Dendritic cells

Other type of white bloods cells, known as neutrophils or granulocytes, they also make up an important part of the immune system. Their role is to fight and kill bacteria.

- Lymphocytes

B cells and plasma cells:

B cells (B Lymphocytes) are made in the bone marrow, which is the spongy inner part of some bones. After they are made, most B Cells move to the lymph nodes, which are bean sized collections of immune system cells found throughout the body. B cells also collect in the lymph tissue contained in some internal organs such as the spleen, Stomach, & Intestines.

B cells can't directly destroy germs or cancer by themselves. But play an important role in immune defences by making antibodies, which are large,sticky proteins. Each antibody is made to attach to certain antigen.

When B cell comes into contact with antigen (on a germ or cancer cell) it starts making antibodies and turn into plasma cell. Plasma cells release anti bodies that bind (attach) only to that antigen. The antibodies then help kill any cells that have the antigen. The antibodies may destroy them directly or they may serve as a marker for other immune system cells, such as T cells, to destroy them.

- T Cells:

Some lymphocytes that are formed in the above marrow enter the bloodstream before they are fully mature. That go to the thymus (a small gland in front of heart and behind the breastbone), where they mature and gain new disease-fighting properties. Once they leave the thymus gland, they are known as T lymphocytes or T cells (named for T in thymus) T cells gather in the lymph nodes and spleen, where they work together with other immune system cells. T cells have special proteins on their surface that allow them to recognize and react to parasites, cancer cells and cells infected by viruses, much like antibodies do.

There are 3 main kinds of TCells. They each have different jobs.

- Killer T Cells (cytotoxic T Lymphocytes) destroy unwanted cells in the body. When these cells come in contact with specific foreign cells they recognise, they give off substances that kill the cells.
- Helper T cell does not directly kill cancer cells or germs, but they release substances that help B cells and killer T Cells work better.
- Regulatory (suppressor) T cells act as brakes to help keep immune system in check. That helps ensure that the immune system does not overreact and attack other healthy parts of the body. These are sometimes called Treg Cells.
- Natural Killer (NK) Cells: Lymphocytes called natural killer (NK) cells are not as picky killer T Cells in what they attack. When fighting cancer, they are drawn to areas with cancer cells by substances given off by other cells. They attach to cancer cells and release substance that split the cells open, killing them. They then look for other cancer cells to attack.
- Antigen – Presenting cells: The main functionof antigen presenting cells (APC) is to help lymphocytes recognize antigens on foreign cells (including cancer cells). Antigen presenting cells include monocytes, macrophages and dendritic cells.
- Monocytes and Macrophages: Monocytes are made by the bone marrow and release into the blood stream. Some monocytes enter tissue and organs. Here they become macrophages, capable of surrounding and eating unwanted cells, they then present antigens from the devoured cells on their outer surface, so that lymphocytes can recognize the foreign antigens if they are found in the body later on. Both monocytes and macrophages can act as APCs to help start an immune response.
- Dendritic Cells: Like monocytes and macrophages,dendritic cells find unwanted cell in the body, chew them up, and present their antigens on their surface. They then travel to an area with many lymphocytes, such as the lymph nodes or spleen. Here they activate certain lymphocytes to go out and attack any similar cells in the body. Dendritic cells are not common, but they are the most powerful type of antigen- presenting cells. Because of this they are the focus of many cancer vaccines currently beingdeveloped.

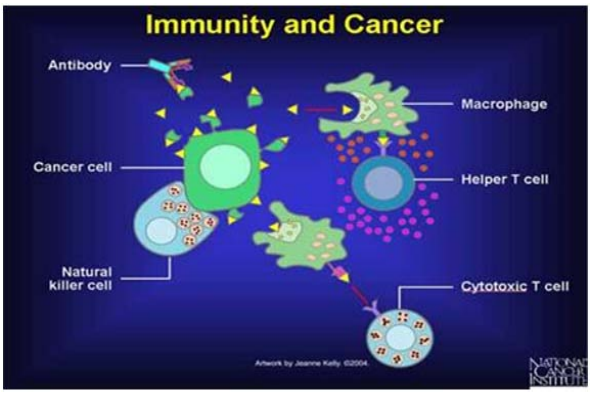
- Type of Immunotherapy: There are good reasons to think the immune system helps in the fighting against cancer. For instance, people with weakened immune systems are more likely to get certain cancers.But many people with normal immune system still develop cancer. This may be because the immune system doesn't see the cancer cells as foreign. Often, this is because the cancer cells (and their antigens) are not different enough from those of normal cells.Sometimes the immune system recognizes the cancer cells, but the response may not be strong enough to destroy the cancer. Cancer cells themselves may also give off substances that keep the immune system in check.To overcome this, researchers have designed ways to help the immune system recognize cancer cells and strengthen its response so that it will destroy the cancer.

Immunotherapy works in 2 ways:

- Active immunotherapies stimulate your body's own immune system to fight the disease.
- Passive immunotherapies use immune system components(such as antibodies) made in the lab.

They do not rely on your body to start the attack on the disease.

Another way that immunotherapies work is by targeting a certain type of cell. Most of the immunotherapies being use today target one kind of cell or antigen (specific immunotherapies), but there are some that stimulate the immune system in general. These are called non-specific immunotherapies. Sometimes non-specific immunotherapies are used with other treatments to help increase the attack on the cancer. These kinds of treatments are generally only used along with treatments, so they are called adjuvants. There are other treatments, called targeted therapies that zero in on one type of cell and don't tend to damage other cells.



Drugs Approved by FDA

Rituximab (Rituxan)

It is a monoclonal antibody that is approved to treat certain type of B-cell non Hodgkin lymphoma and when combined with other drugs, to treat chronic lymphocytic leukaemia (CLL). The therapy recognizes a molecule called CD20 that is found on B cells. When rituximab binds to these cells, it triggers an immune response that results in their destruction. Rituximab may also induce apoptosis.

Alemtuzumab (Campath):

It is approved to treat patients with B cell CLL. The therapy is a monoclonal antibody directed against CD52, protein found on the surface of normal and malignant B & T cells and many other cells of the immune system. Binding of alemtuzumab to CD52 triggers an immune response that destroys the cells.

Ofatumumab (Arzerra):

It is approved for the treatment of some patients with CLL that does not respond to treatment with Ofludarabine and alemtuzumab. This monoclonal antibody is directed against the B cell CD20 cell surface antigen.

Ipilimumab (Yervoy):

It is approved to treat patients with metastatic melanoma. This monoclonal antibody is directed against cytotoxic T lymphocyte-associated antigen-4(CTLA-4), which is expressed on the surface of activated T cell as part of a "checkpoint" to prevent a runaway immune response. By inhibiting CTLA-4, ipilimumab stimulates the immune system to attack melanoma cells.

Apoptosis: [4, 13]

Apoptosis is a multi-step, multi pathway cell death programme that is inherent in every cell of the body. In cancer, the apoptosis cell-division ratio is altered. Cancer treatment by chemotherapy and radiation kills target cells primarily by inducing apoptosis.

Apoptosis, or programmed cell death, is highly regulated process that allows a cell to self-degrade in order for the body to eliminate unwanted or dysfunctional cells. During Apoptosis, the genome of the cell will fracture, the cell will shrink and part of the cell will disintegrated into smaller Apoptotic bodies. Unlike necrosis , where the cell dies by swelling and bursting its content in the area, which causes an inflammatory response , Apoptosis is a very clean and controlled process where the content of the cell is kept strictly within the cell membrane as it is degrade. The Apoptotic

cell will be phagocytised by macrophages before the cells contents have a chance to leak into the neighbourhood. Therefore, Apoptosis can prevent unnecessary inflammatory response.

Inhibition of Apoptosis:

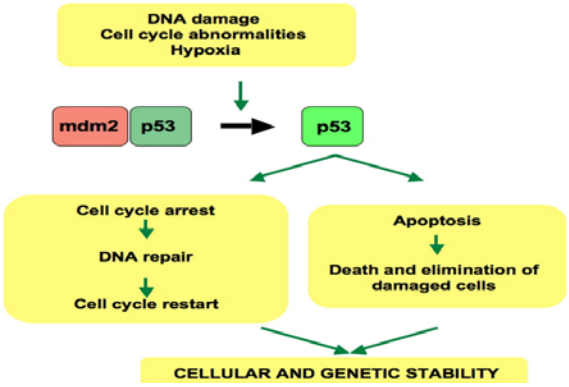
Inhibition of Apoptosis can result in a number of cancers, autoimmune disease, inflammatory disease, and viral infections. It was originally believed that the associated accumulation of cells was due to an increase in cellular proliferation, but it is now known that it is also due to a decrease in cell death. The most common of these diseases is cancer, the disease of excessive cellular proliferation, which is often characterized by an over expression of IAP family members. As a result, the malignant cells experience an abnormal response to Apoptosis induction: cycle regulating genes (such as p53, ras or c-myc) are mutated or in activated in diseased cells, and further genes (such as bcl-2) also modify their expression in tumor.

p53:

P53 has many mechanisms of anticancer function, and plays a role in Apoptosis, genomic stability, and inhibition of angiogenesis. In its anti- cancer role, p53 works through several mechanisms:

- It can activate DNA repairs proteins when DNA has sustained damage.
- It can induce growth arrest by holding the cell cycle at theG1/S regulation point on DNA damage recognition (if it holds the cell here for long enough, the DNA repairs proteins will have time to fix the damage and the cell will be allowed to continue the cell cycle.)
- It can initiate Apoptosis, the programmed cell death, if DNA damage proves to be irreparable.

p53 pathway: In a normal cell p53 is inactivated by its negative regulator, mdm2. Upon DNA damage or other stresses, various pathways will lead to the dissociation of the p53 and mdm2 complex. Once activated, p53 will induce a cell cycle arrest to allow either repair or survival of the cell or Apoptosis to discard the damaged cell. How p53 make this choice is currently unknown. Activated p53 binds DNA and activates expression of several genes including WAF1/ CIP1 encoding for p21. P21 (WAF1) binds to the G1-S/CDK(CDK2)and S/CDK complexes (molecules important for the G1/S transition in the cell cycle) inhibiting their activity.



When p21 (WAF1) is complexed with CDK2 the cell cannot continue to the next stage of cell division. A mutant p53 will no longer bind DNA in an effective way, and, as a consequence, the p21 protein will not be available to act as the "stop signal" for cell Division. This, cells will divide uncontrollably, and form tumor.

Recent research has also linked the p53 and RB1 pathways, via p14ARF, raising the possibility that the pathways may regulate each other. P53 by regulating LIF has been shown to facilitateimplantation in the mouse model and possibly in humans. P53 expression can be stimulated by UV light, which also causes DNA damage. In this case, p53 can initiate events leading to tanning.

Treatments by Inhibiting or increase Apoptosis in disease: [4, 14]

The main method of treatment for death signalling-related diseases involved either increasing or decreasing the susceptibility of Apoptosis in diseased cells, depending on whether the disease is caused by either the inhibition of or excess Apoptosis. For instance, treatments aim to restore Apoptosis to treat diseases with deficient cell death, and to increase the Apoptosis threshold to treat diseases involved with excessive cell death. To stimulate Apoptosis, one can increase the number of death receptor ligands(such as TNF or TRAILS) , antagonize the anti-apoptotic Bcl-2 pathway, or introduce Smacmimetics to inhibit the inhibitor (IAPs). The addition of agents such as Herceptin, Iressa or Gleevec works to stop cells from cycling and causes Apoptosis activation by blocking growth and survival signalling further upstream. Finally, adding p53-MDM2 complexes displaces p53 and activates the p53 pathway, leading to cell cycle arrest and Apoptosis. Many different methods can be used to stimulate Apoptosis in various places along the death signalling pathway.

Cancer:

Cancer may arise from the dysfunction in the Apoptosis pathway. Due to the sensitivity of the intrinsic pathway, tumor arises more often through the intrinsic pathway than the extrinsic pathway. In intrinsic pathway, a very common cause of tumorgenesis is mutation of the p53 protein. Besides regulating Apoptosis, p53 also regulates the check points in the cell cycle, DNA repair, senescence and genomic integrity. Any mutation that causes p53 to lose any of its function will induce tumorgenesis by letting the cell grow indefinitely without any regulation. Another important factor in tumorgenesis is the balance between the pro Apoptotic members of Bcl 2 family. In a tumor cell, a mutation of Bcl 2 gene that results in increased expression will suppress the normal function of the pro Apoptotic proteins, BAX and BAK. On the other hand, if a mutation on the BAX or BAK genes causes a down regulation of expression that the cell will also lose its ability to regulate apoptosis, again causing tumorgenesis.

Drugs approved by FDA

Bortezomib (Velcade)

It is approved to treat some patients with multiple myeloma. The drug is also approved for the treatment of some patients with mantle cell lymphoma. Bortezomib causes cancer cells to die by interfering with the action of a large cellular structure called the proteasome, which degrades proteins. Proteasomes control the degradation of many proteins that regulate cell proliferation. By blocking this process, bortezomib causes cancer cells to die. Normal cells are affected too, but to a lesser extent.

Pralatexate (Folotyn)

It is approved for the treatment of some patients with peripheral T-cell lymphoma. Pralatrexate is an antifolate, which is atype of molecule that interferes with DNA synthesis. Other antifolate, such as methotrexate is not considered targeted therapies because they interfere with DNA synthesis in all dividing cells. However, pralatrexate appears to selectively accumulate in cells that express RFC-1, a protein that may be overexpressed by some cancer cells.

GENE EXPRESSION: [6]

Gene expression profiling is a technique used in molecular biology to query the expression of thousands of genes simultaneously. While almost all cells in an organism contain the entire genome of the organism, only a small subset of those genes is expressed as messenger RNA (mRNA) at anygiven time, and their relative expression can be evaluated. Techniques include DNA microarray technology or sequenced-based techniques such as serial analysis of genes expression (SAGE). Current cancer research makes use primarily of DNA microarrays in which an arrayed series of microscopic spots of pre-defined DNA oligonucleotides known as probes are covalently attached to a solid surface such as glass, forming what is known asa gene chip. DNA labelled with fluorophores (target) is prepared from a sample such as a tumor biopsy and is hybridized to the complementary DNA (cDNA) sequence on the gene chip. The chip is then scanned for the presence and strength of the fluorescent labels at each spot representing probe-target hybrids. The level of fluorescence at a particular spot provides quantitative information about the expression of the particular gene corresponding to the spotted cDNA sequence. DNA microarrays evolved from Southern blotting which allows for detection of a specific DNA sequence in a sample of DNA.

The genetic changes involved in cancer result in altered proteins that disrupt the cell's communication network. In cancer, altered proteins along many different pathways cause signals to be garbled, intercepted, amplified, or misdirected. These changes hijack what was once normal communication and use it to achieve uncontrolled tumor growth.

Drugs Approved by FDA [6]

Vorinostat (zolinz)

It is approved for the treatment of cutaneous T – cell lymphoma (CTCL) that has persisted, progressed, or recurred during or after treatment with other medicines. This small-molecular drug inhibits the activity of agroup of enzymes called histone deacetylases (HDACs), which remove small chemical group called acetyl groups from many different proteins, including proteins that regulate gene expression. By altering the acetylation of these proteins, HDAC inhibitors can induce tumor cell differentiation, cell cycle arrest, and apoptosis.

Romidepsin (istodax)

It is approved for the treatment of CTCL in patients who have received at least oneprior systemic therapy. This small-molecule drug inhibits members of one class of HDACs and induces tumor cell apoptosis.

Bexarotene(Targretin)

It is approved for the treatment of some patients with CTCL. This drug belongs to a class of

compounds called retinoids, which are chemically related to vitamin A. Bexarotone binds selectively to, and thereby activates, retinoid X receptors. Once activates, these nuclear proteins act in concert with retinoic acid receptors to regulate the expression of genes that control cell growth, differentiation, survival, and death.

Alitretinoin (Panretin)

It is approved for the treatment of cutaneous lesions in patients with AIDS-related Kaposi sarcoma. This retinoid binds to both retinoic acid receptors and retinoid X receptors.

Tretinoin (Vesanoid)

It is approved for the induction of remission in certain patients with acute promyelocyticleukemia. This retinoid binds to and thereby activities retinoic acid receptors.

Future Consideration [7, 8]

Biological Therapies:

- **Monoclonal antibodies**- targeted therapies include monoclonal antibodies that deliver toxic molecular to cancer cells specifically.
- **Cancer vaccines**- contain information on vaccines intended to treat cancer.
- **Gene therapy** – gene therapy for cancer discusses research with genetic material in developing cancer therapies, including risks, benefits and ethical issues.

Monoclonal antibodies- targeted therapies

Cancer is one of the most common causes of death, taking nearly 7 million lives each year worldwide. New cancer targeted therapies that make use therapeutic antibodies or small molecules have made treatment more tumor specific and less toxic. Nevertheless, there remain several challenges to the treatment of cancer, including drug resistance, cancer stem cells, and high tumor interstitial fluid pressure. In many solid tumor, for example, increased interstitial fluid pressure makes the uptake of therapeutic agents less efficient. One of the most promising ways of meeting such challenges is ligand-targeted therapy that may be used to male targeting more specific more and carry higher dosages of anti-cancer drug to tumor tissue.

Monoclonal Antibody:

In 1975, Kohler & Milstein developed techniques for producing MoABs , making it possible to produce large quantities of identical antibodies directed against specific antigens. Antibodies, which initially were viewed as "targeting missiles", have proved much more complex in their targeting and biologic properties than the field's pioneers envisioned them MoABs have emerged as important therapeutic agents for several different malignancies; they have been found to be well-tolerated and effective for the treatment of different cancers, and were consequently approved by the FDA of the US. In addition to their own role as anticancer agents, their ability to target tumor also enables them to improve the selectivity of other type of anticancer agents, some of which cannot be applied effectively alone. Murine antibody can be readily transformed into human or humanized format that are not readily recognized as foreign by human immune system. In addition, novel antibody based structures with multiple antigen recognition sites, altered size, or effector domains have been shown to influence the targeting ability of antibodies. Couple with the identification of appropriate cancer targets, antibody based therapeutics are finding increasing number of application in cancer treatment, and they can be effective alone, in conjunction with chemotherapy or radiation therapy, or when conjugated to toxic moieties such as toxins, chemotherapy agents, or radionuclides.

Therapeutic antibodies for cancer:

The first chimeric antibodies were generated in the late 1980s and in 1997 the first therapeutic antibodies, rituximab (RITUXAN; Genentch / Biogen Idec) was approved by the US FDA for the treatment of B cell non-Hodgkin's lymphoma. Since then, MoAb based therapies have become a major strategy in medicine. In fact, approximately a 25-30 % of all biotechnology products being developered are MoAbs and several have now been approved by the US FDA for the treatment of cancer. Trastuzumab (herceptin;Genentch) was approved by the US FDA for use in patients with metastaic breast cancer in 1998. It is a genetically engineered anti HER2 monoclonal antibody that inhibits proliferation in vitro of tumor cells, overexpressing HER 2 protein and specifically targets the HER2 oncoprotein. The HER2 protein is produed in excessive amounts in 25-30% of patients with breast cancer and isassociated with aggressive growth to tumor cells. Trastuzumab was humanized by adding the critical mouse recognition sequence to the framework of human IgGi to maximize immume recruitment. The reduction of murine components (95% human and 5% murine) decreases the potential for immunogenicity that is seen with murine monoclonal antibody therapy and increase the potential for recruiting immune mechanisms.

Bevacizumab (avastin; Genentch) was approved by US FDA as a first- line treatment for patients with metastaic colorectal cancer on february 2004. The median duration of survival was 20.3 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus Avastin, as compared with 15.6 months in the group given IFL plus placebo (increase of 4.7 months) in a phase III trail with metastatic colorectal cancer. In 1993, it was shown that a monoclonal antibody that targeted VEGF resulted in adramatic suppression of tumor growth in vivo, which led to the development of bevacizumab by the US FDA supports the ideas that VEGF is a key mediator of tumor angiogenesis and that blocking angiogenesis is an effective strategy for treating cancer in humans. The potential clinical utility of VEGF inhibition in oncology is not limited to solid tumor. There is growing evidence that VEGF receptors are expressed by a variety of leukaemia's and other haematological malignancies, indicating that inhibition of VEFG or VEGFR signalling might play a role in the treatment of such conditions. However, in February 2006 the pharmaceutical manufacturer stopped recruiting patients for testing Avastin in late stage clinical trails after sudden deaths of four deaths of four patients,especially in three younger patients.

Targeted Therapy by small molecules:

Glivec (imitanibmesylate, Gleevec, STI571; Novartis) is the first selective tyrosine kinase inhibitor to be approved for the treatment of cancer in 2001 .Glivec is a@ phenylaminopyrimidine which completitively inhibits ATP binding to tehAbl kinase, thereby inhibiting the constitutively activated Bcr-Abl tyrosine kinase, which is a specific genetic change encoding abnormal protein associated with human cancer. As the tyrosine kinase activity of Bcr-Abl is crucial for its transforming activity, the enzymatic activity of this deregulated gene could plausibly be defined as an attractive drug target for addressing Bcr-Abl-related chronic myelogenous leukaemia (CML). In an in vitro screen against a panel of protein kinases, Glivec was found to inhivit the auto-phosphorylation of there kinases: Bcr-Abl, c-Kit and platelet-derived growth factor (PDGF) recaptor. More recently, activity against ARG kinase has alos been reported. Glivec can be used to treat CML, gastrointestinal stromal cell tumors (GIST) and metastatic dermatofibrosacomaprotuberans, afflictions that ate associated with the expression and activity of these kinases. CML represents the first human cancer in which molecularly targeted therapy was reported to lead to a dramatic clinical response. Glivec has also been used in clinical trials for other type of cancers overexperssing related proteins, but the results did not show significant clinical activity , further confirming the collective evidence that prediction of efficancy of novel therapeutic agents is based on target expression rather than on pathway activation (for example, through activating mutations). Gefitnib (Iressa; AtraZeneca Pharmaceuticals), a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, has been found to disrupt EGFR kinase activity by binding the ATP pocket within the catalytic domain .Gefitinib has also been repoted to prevent EGFR phosphorylation, decrease mitogen-activated protein kinase activity, increase apoptosis, and also increase levels of the cyclin-dependent kinase inhibitor p27 which is believed to lead to G1 cell cycle arrest.

Mechanism of action of small molecule inhibitors for tumor treatment

Most of the small molecule inhibitors are designed to specifically target overexpressed on mutaed signalling pathways in tumor cells rather than normal cells, and then, the life cycle of tumor cells will be blocked and triggered to apoptosis. Activated Bcr-Abltyrosins kinase cause chronic myelogenous leukaemia (CML) The activity of Bcr-Abl is catalyzed by ATP, and the phosphorylation binding site can be inhibited by glivec. Therefore, the tumor cells proliferation will be terminated and alternatively switch to apoptosis pathway.

Drug approved by FDA:

Tositumomab& 131I- tositumomab (Bexxar)

It is approve to treat certain type of B-cell non-Hodgkin lymphoma. The therapy is a mixture of monoclonal antibodies that recognize the CD20 molecule. some of the antibodies in the mixture are linked to a radioactive substance called iodine-131. The 131I-tositumomab component delivers radioactive energy to CD20-expressing B-cell specifically, reducing collateral damage to normal cells. In addition, the binding of tositumomab to the C20-expression B cells triggers the immune system to destroy these cells.

Ibritumomabtituxetan (Zevalin)

It is approved to treat some patients with B-cell non-Hodgkin lymphoma. The therapy is a monoclonal antibody directed against CD20 that is linked to a molecule that can bind radioisotopes such as indium-111 or yttrium-90. The radiolabel

forms of zevalin deliver a high dose of radioactive to cells that express CD20.

Vaccines [9, 10]

Vaccines have been used for many years as a way of preventing infectious illnesses such as flu, tuberculosis (TB), measles, mumps, typhoid and German measles. Vaccines stimulate the body's immune system to recognise and fight abnormal 'foreign' cells in the body, such as viruses and bacteria.

Scientists and doctors are now trying to develop vaccines that can stimulate the immune system to recognise and destroy cancer cells. Some vaccines for particular cancers have been developed and arebeing tested to see whether they can treat the cancer or help stop it from coming back after treatment.

The immune system

Our immune system protects us from infection and disease. It is a complex system made up of the bone marrow, the thymus gland (which lies behind the breast bone), the spleen and the lymph nodes (or lymph glands). One of the most important cells in our immune system is a type of white blood cell called a lymphocyte. These are made in the bone marrow and circulate around the body in the blood and lymph vessels. They recognise unwanted or abnormal cells and act quickly to destroy them. There are two types of lymphocytes: B-cells and T-cells. B-cells develop into plasma cells that make specialised proteins called antibodies. Antibodies circulate in the blood and react with toxins, bacteria and some cancer cells. The body can then identify and remove these unwanted cells. However, some foreign substances in the body can hide from the B-cells by growing within the body's own cells. T-cells can sense when the body's own cells have become abnormal and can destroy them. The whole process is known as an immune response. After the abnormal cells or bacteria have been destroyed, the surviving B-cells and T-cells develop into specialised memory cells. They remain on watch in the lymph nodes and are reactivated if that particular abnormal cell or substance appears in the body again abnormal cell or substance appears in the body again.

The immune response

Abnormal cells usually have proteins (antigens) on their surface. The T-cells and B-cells recognise these proteins as foreign or abnormal.

The B-cells produce antibodies. The antibodies attach to the antigens and attract the T-cells. Together they destroy the abnormal cells.

Cancer and the immune system

The human body is made up of tiny building-blocks called cells. Cells look and function differently throughout the body, but reproduce and repair themselves in the same way. This process normally happens in an organised and controlled manner. If cells become cancerous they start to divide in an uncontrolled way and don't die when they should.

The immune system sometimes has difficulty recognising cancer cells and doesn't destroy them. The cancer cells then continue to grow.

The aim of cancer vaccines

The aim of cancer vaccines is to stimulate the immune system to be able to recognise cancer cells as abnormal and destroy them.

How cancer vaccines are made

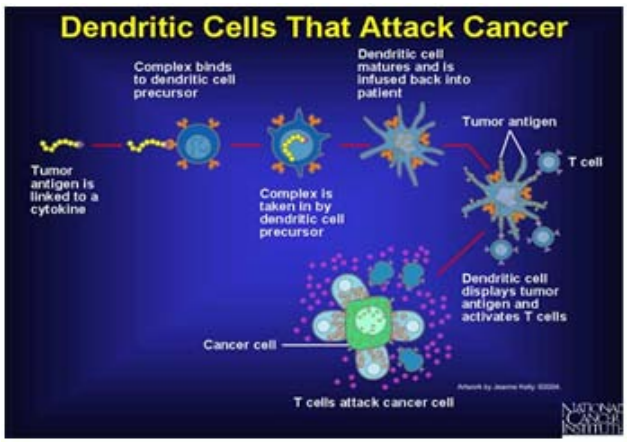
Cancer vaccines are made from the person's own cancer cells or from cells that are grown in a laboratory.

The cancer cells are treated with heat or radiation. This is so that they cannot multiply and grow and tomake sure that they cannot cause harm.

Certain proteins may then be taken from the cancer cells and used to make a cancer vaccine. These include antigens, which are the proteins on the cell surface that can stimulate an immune response. Sometimes, whole cells may be used to make the vaccine.

Often a cancer vaccine will also contain substances that are already known to boost the immune system, such as BCG (the vaccine that protects against tuberculosis).

As the cancer vaccine contains similar proteins to the cancer cells, it's hoped that the immune system will be stimulated to attack and destroy them.



How cancer vaccines are given

Cancer vaccines are usually a liquid that's given by an injection under the skin. How often they are given will depend on the type of cancer being treated and the type of vaccine being used.

Possible side effects

The possible side effects of cancer vaccines include a skin reaction at the injection site, a skin rash or mild flu-like symptoms. Certain cancer vaccines may cause more specific symptoms and you should be told about these by your nurse or doctor before starting treatment.

Research trials

Vaccines are being used in research trials. When a new treatment is being developed it needs to go through various stages of research called clinical trials.

Most trials with cancer vaccines are treating people with advanced cancers that can't be cured. However, some research is looking at treating cancers at an earlier stage. It's possible that vaccines may be used to try to prevent cancers at some time in the future.

Currently most of the research into vaccines has looked at cancer of the prostate gland, breast, pancreas, colon and rectum, lung, skin (mainly malignant melanoma), kidney, ovary, bladder and cervix. Vaccines have also been used to treat lymphoma and leukaemia.

Cancer gene therapy: [6, 11]

Cancer occurs by the production of multiple mutations in a single cell, that causes it to proliferate out of control. Cancer cells often different from their normal neighbours by a host of specific phenotypic changes, such as rapid division rate, invasion of new cellular territories, high metabolic rate, and altered shape. Some of those mutations may be transmitted from the parents through the germ line. Others arise de novo in the somatic cell lineage of a particular cell. Cancer-promoting mutations can be identified in a variety of ways. They can be cloned and studied to learn how they can be controlled.

Several methods such as surgery, radiation, and chemotherapy have been used to treat cancers. The cancer patients who are not helped by these therapies may be treated by gene therapy. Gene therapy is the insertion of a functional gene into the cells of a patient to correct an inborn error of metabolism, to alter or repair an acquired genetic abnormality, and to provide a new function to a cell. Two basic types of gene therapy have been applied to humans, germinal and somatic. Germinal gene therapy, which introduces transgenic cells into the germ line as well as into the somatic cell population, not only achieves a cure for the individual treated, but some gametes could also carry the corrected genotype. Somatic gene therapy focuses only on the body, or soma, attempting to effect a reversal of the disease phenotype by treating some somatic tissues in the affected individual.

One of the most promising approaches to emerge from the improved understanding of cancer at the molecular level is the possibility of using gene therapy to selectively target and destroy tumor cells, for example, the loss of tumor suppressor genes (e.g. the P53 gene) and the over expression of oncogenes (e.g. K-RAS) that have been identified in a number of malignancies. It may be possible to correct an abnormality in a tumor suppressor gene such as P53 by inserting a copy of the wild-type gene; in fact, insertion of the wild-type P53 gene into P53-deficient tumor cells has been shown to result in the death of tumor cells. This has significant implications, since P53 alterations are the most common genetic abnormalities in human cancers. The over expression of an oncogene such as K-RAS can be blocked at the genetic level by integration of an antisense gene whose transcript binds specifically to the oncogene RNA, disabling its capacity to produce protein. Experiments in vitro and in vivo have demonstrated that when an antisense K-RAS vector is integrated into lung cancer cells that over express K-RAS their tumorigenicity is decreased.

Despite the promise of such approaches, a number of difficulties remain to be overcome, the most important of which is the need for more efficient systems of gene delivery. No gene transfer system is 100% efficient, unless germ-line therapy is contemplated. During the past two decades, there have been major advances in our understanding of how cancer develops, proving that cancer has a genetic basis. 0A series of genetic abnormalities that accumulate in one cell may result in a pattern of abnormal clonal proliferation. Our growing understanding of the genetic basis of cancer offers new opportunities for the molecular prevention and treatment of cancer. There has been a substantial growth in gene therapy, especially in the field of oncology since the first experiment in human gene therapy began in 1990 (5), with the aim of treating adenosine deaminase deficiency. By the end of 1993, there were 45 approved trials by US Recombinant DNA Advisory Committee, 30 of which are for the treatment of cancer. This is, in part, became tumor cells can be manipulated ex vivo, while the affected tissues from individuals with other genetic diseases often cannot.

Strategies of gene therapy for cancer: [6]

1. Enhancing the immunogenicity of the tumor, for example by introducing genes that encode foreign antigens.
2. Enhancing immune cells to increase anti-tumor activity, for example by introducing genes that encode cytokines.
3. Inserting a "sensitivity" or suicide' gene into the tumor, for example by introducing the gene that encodes HSVtk.
4. Blocking the expression of oncogenies, for example by introducing the gene that encodes antisense K-RAS message.
5. Inserting a wild-type tumor suppressor gene, for example P53 or the gene involved in Wilm' tumor.
6. Protecting stem cells from the toxic effects of chemotherapy, for example by introducing the gene that confers MDR-1.
7. Blocking the mechanisms by which tumors evade immunological destruction, for example by introducing the gene that encodes antisense IGF-1 message.
8. Killing tumor cells by inserting toxin genes under the control of a tumor-specific promoter, for example the gene that encodes diphtheria A chain.

CONCLUSION

Targeted cancer therapies also holds the promise of being more selective for cancer cells than normal cells, thus harming fewer normal cells, reducing side effects, and improving quality of life. By focusing on molecular and cellular changes that are specific to cancer, Targeted cancer therapies may be more effective than other types of treatment, including chemotherapy & radiotherapy as are less harmful to normal cells. Most targeted therapies are either small-molecule drugs or monoclonal antibodies. Small-molecule drug are typically able to diffuse into cells and can act on targets are found inside the cell. Targeted therapy refers to a new generation of cancer drugs designed to interfere with a specific target protein that is believed to have a critical role in tumor growth or progression. The molecular identification of cancer antigens has opened new possibilities for the development of effective immunotherapies, antibodies therapy and ligand-targeted therapy for cancer patients.

ACKNOWLEDGEMENT

The authors are thankful to Hyderabad (Sind) National Collegiate Board and Dr. P.S.Gide, Principal, H(S)NCB's Dr. L. H. Hiaranandani College of Pharmacy for their constant support and Guidance.

REFERENCES

1. MalinDollinger, M.D, Ernest H. Rosenbaum. Everyone's guide to CANCER THERAPY, Canadian Medical Association.
2. American cancer society. Traditional treatment for Cancer. http://www.cancer.org/
3. Fisher B, costantino JP, Wickerham DL, et al: P-1 study. Tamoxifen for prevention of brest cancer: report of the National surgical Adjuvant Brest & bowel Project. J Natl Cancer Inst. 1998;90: 1371-1388.
4. Gael McGill & David E.Fisher. Apoptosis in Tumorigenesis& Cancer therapy, Division of PediatricHematology/oncology, Dana Farbe Cancer Institute & Children Hospital, Harvard Medical School, 44 Binney St, Boston, Ma 02115
5. Han-Chung Wul, De-kaun Chang & chia-Ting, & Chia-ting Huang, Targeted Therapy for Cancer, Institute of Cellular & Organismic Biology, Acadamiasinica, Taipei, Taiwan.
6. Handbook Help me Understand Genetics, Gene Therapy, Lister Hill National Centre for Biomedical, Communication U. S National Library of Medicine National institutes of Health Department of Health &hUman services U.S.
7. Sangaller ML. Rosenberg SA. Principles & Practice of the Biologic Therapy of Cancer, Lippincott Williams & Wilkins; 200:584-601.
8. National Cancer Institute, U.S department of Health & Humane sercice Reviewed: 18/11/2011
9. DeVita V, et al. Cancer - Principles and Practice of Oncology. 8th edition. 2008. Lippincott Williams & Wilkins. Sikora, et al. "Treatment of Cancer". 5th edition. 2008. Hodder Arnold.
10. Han-Chung Wu1, Chia-Ting Huang, and De-Kuan Chang. Anti-Angiogenic Therapeutic Drugs for Treatment ofHuman Cancer. Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan.
11. Lugo TG, Pendergast AM, Muller AJ, Witte ON. Tyrosine kinaseactivity and

transformation potency of bcr-abl oncogene products.
12. Faivre S, Demetri G, Sargent W, Raymond E. Molecular basis forsunitinib efficacy and future clinical development. Nat Rev DrugDiscov 6: 734-745, 2007.Science 247: 1079-1082, 1990.
13. www.cancer.gov/newscenter/angio.
14. www.nucleusinc.com.