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ANTICANCER DRUGS

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ABSTRACT

Cancer is often thought of as an untreatable, unbearably painful disease with no cure. However popular this view of cancer may be, it is exaggerated and over-generalized. Cancer is undoubtedly a serious and potentially life-threatening illness. However, it is a misconception to think that all forms of cancer are untreatable and deadly. While a diagnosis of cancer may still leave patients feeling helpless and out of control, in many cases today there is cause for hope rather than hopelessness. Cancer is a disease characterized by uncontrolled, uncoordinated and undesirable cell division. Unlike normal cells, cancer cells continue to grow and divide for their whole lives, replicating into more and more harmful cells. The abnormal growth and division observed in cancer cells is caused by damage in these cells' DNA (genetic material inside cells that determines cellular characteristics and functioning). There are a variety of ways that cellular DNA can become damaged and defective. Anti-Cancer drugs are medicines formulated to treat wide range of cancer. Cancer is the uncontrolled growth of cells that interfere with the growth of healthy cells. The usual treatments of Cancer are surgery, chemotherapy (treatment with anticancer drugs), radiation, or some combination of these methods. Anti-Cancer drugs are targeted to control and treat various Cancer like, Breast cancer, Cervical cancer, Small cell lung cancer, Head and Neck cancer, Ovarian cancer, Hodgkin's and Non-Hodgkin's lymphoma, Oesteo-sarcoma, Seminomas of testis, Myeloblastic leukemia, Lymphoblastic leukemia etc. The use and application of drugs synthesized or procured from natural or synthetic sources for cancer inhibition and cure is known as "chemotherapy" and the drugs are more commonly named as chemotherapeutic drugs.

Keywords: Normal cells, cancer cells, tumour, causes and treatment of cancer.

INTRODUCTION

Cancer [1-3] occurs after normal cells have been transformed into neoplastic cells through alteration of their genetic material and the abnormal expression of certain genes. Neoplastic cells usually exhibit differentiated properties. These changes lead to uncontrolled cells division and many result in the invasion of previously unaffected organs, a process called metastasis cancer, in medicine, common term for neoplasms, or tumors, that are malignant. Like benign tumors, malignant tumors do not respond to body mechanisms that limit cell growth. Unlike benign tumors, malignant tumors consist of undifferentiated, or unspecialized, cells that show an atypical cell structure and do not function like the normal cells from the organ from which they derive. Cancer cells, unlike normal cells, lack contact inhibition; cancer cells growing in laboratory tissue culture do not stop growing when they touch each other on a glass or other solid surface but grow in masses several layers deep.

Loss of contact inhibition [2-4] accounts for two other characteristics of cancer cells: invasiveness of surrounding tissues, and metastasis, or spreading via the lymph system or blood to other tissues and organs. Whereas normal cells have a limited lifespan controlled by the telomere gene, which signals the end of the cell line, cancer cells contain telomerase, an enzyme that alters the telomere gene and allows the cell to continue to divide. Cancer tissue, growing without limits, competes with normal tissue for nutrients, eventually killing normal cells by nutritional deprivation. Cancerous tissue can also cause secondary effects, in which the expanding malignant growth puts pressure on surrounding tissue or organs or the cancer cells metastasize and invade other organs.

Virtually all organs and tissues are susceptible to cancer. Cancers are usually named for their site of origin. Cancer cells that spread to other organs are similar to those of

the original tumor therefore these secondary (metastatic) cancers are still named for their primary site even though they may have invaded a different organ. For example, lung cancer that has spread to the brain is called metastatic lung cancer, rather than brain cancer. Carcinoma *in situ* refers to a cancer that has not spread. Cancer is the second leading cause of death in the United States. Lung cancer is the leading cause of cancer death in adults; leukemia is the most common cancer in children. Other common types of cancer include breast cancer (in women), prostate cancer (in men), and colon cancer. The incidence of particular cancers varies around the world and sometimes according to ethnic group. For instance, African Americans have comparatively higher cancer rates and cancer mortality rates. It is unclear whether this is due to differences in exposure or to biological susceptibility. The number of diagnosed cases of cancer rose steadily in the United States for decades, but in 1998 it was announced that the number of new cases had begun to decline [1, 4-6].

The available anticancer drugs have distinct mechanisms of action which may vary in their effects on different types of normal and cancer cells. A single "cure" for cancer has proved elusive since there is not a single type of cancer but as many as 100 different types of cancer. In addition, there are very few demonstrable biochemical differences between cancerous cells and normal cells. For this reason the effectiveness of many anticancer drugs is limited by their toxicity to normal rapidly growing cells in the intestinal and bone marrow areas. A final problem is that cancerous cells which are initially suppressed by a specific drug may develop a resistance to that drug. For this reason cancer chemotherapy may consist of using several drugs in combination for varying lengths of time [1,2].

The role of hormones and the lymphatic system [4, 5-7]

Our hormones carry messages to our cells, triggering the cells to take action. These messages are carried by our blood through our vascular system (arteries, veins and capillaries).

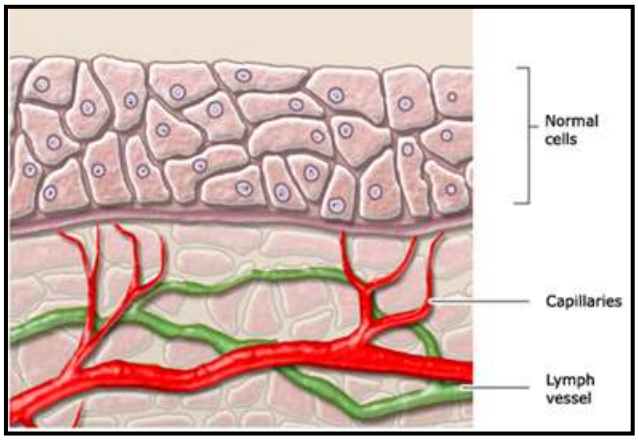

Figure 1: Normal cells

The blood carries the other things that cells need to function too. Our cells need oxygen and glucose to keep them alive, for example. Our blood vessels also carry away waste products and oxygen-poor blood once the cells have used the oxygen in the blood. Our lymphatic system helps to clean and drain what we do not need. The lymphatic system is a part of our body's defence system (immune system), and it drains away bacteria and germs.

Benign and malignant growth

Cells become abnormal [3, 6, 7-9] if their DNA – and therefore their "knowledge" – becomes damaged. As long as there are very few abnormal cells and they are kept under control by our immune system, they will not harm us. It is only when these cells start to divide uncontrollably, forming lumps or growths, that we have one of the more than 200 diseases called cancer. Growths like this are called tumours.

The main differences between malignant (cancerous) and benign (non-cancerous) tumours are that malignant ones can

- spread into the surrounding tissue,
- destroy the surrounding tissue, and
- Cause other tumours to develop.

Malignant tumours can be life-threatening. But there are also some kinds of cancer that develop so slowly in older people that they do not lead to any problems in their lifetime.

Benign tumours usually do not cause much damage and are not normally life-threatening. But there is no guarantee: benign growths can become dangerous if they grow a lot, or they might become malignant after a certain amount of time.

If cancer cells start replicating, they do not behave like normal cells. For example, they do not know when to stop replicating and when to die. And they do not always stick together, so they might break away and move through the vascular or lymphatic system and start growing somewhere else in the body.

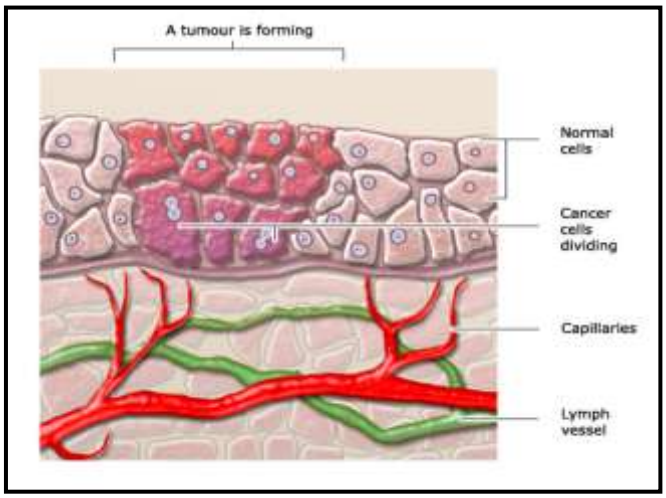

Figure 2: Tumour forming cells and cancer causing cells

When a malignant tumour is contained within one area and has not spread to the surrounding tissue, like the one in the picture above, the medical term is "carcinoma in situ." If this tumour does not keep growing, that means it is just lying there quietly ("dormant cancer cells"). It is not likely to cause harm unless it starts growing.

To keep growing, these tumours start to create their own blood vessels to supply them with the extra oxygen, glucose and hormones they need to survive and keep getting bigger. That process of developing a blood supply system is called angiogenesis (the growth of new blood vessels). Once a tumour does this, it can start to invade the surrounding tissue. This is called an invasive cancer,

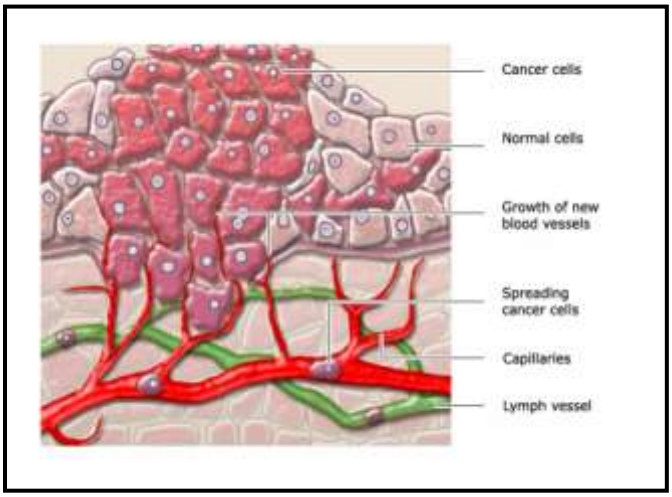

Figure 3: Spreading cancer cells and formations of new blood vesseles

Active cancer cells can enter the bloodstream or lymphatic system and move to other parts of the body to start the process of forming a tumour all over again somewhere else (metastatic or secondary cancer) [3-5].

How do cancer cells grow and spread?

The human body is made up of billions of cells. Cells are the tiny building blocks of our tissues and organs. We all started life as a single cell. That cell made an internal copy of it (replication) and then divided into 2 cells.

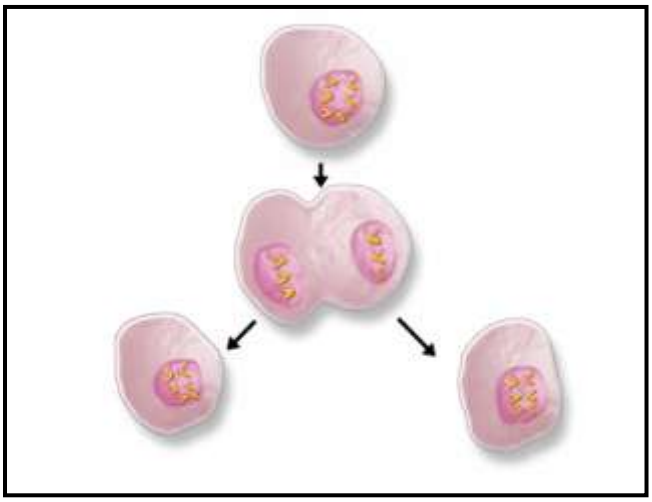

Figure 4: How do cancer cells grow and spread?

Those 2 cells then also replicated and divided, so the two cells became four cells. The four cells replicated as well and divided into eight cells, and so on.

Cells specialize to perform particular tasks. Some cells will cluster together to form a finger, for example. Others create skin and heal the skin when it is wounded. Cells get old and die after a certain amount of time ("programmed cell death, "or apoptosis), and replication ensures that new cells are made to take their place.

When they are acting normally, cells "know" which other cells to join up with and stick to – and they also know when to stop replicating and die. Each type of cell has a particular role and set of knowledge or instructions in their DNA (genes). Our cells know how to make the right number of fingers on our hand for us (and they know that fingers should only grow on our hands).

Each finger is covered with skin and each finger has a fingernail. If we cut our finger, the skin cells will start replicating and create new skin to heal the wound. If we lose a fingernail, our cells can grow a new one. But the cells will not create extra fingers, even if we lose one. The rules are clear for those cells, and they keep to the rules

What are cells?

Normal body cells

The body [5-8] is made up from millions of tiny cells. Different parts of the body such as organs bones, muscles,skin,and blood are made up from different specialised cells. Most cells have a centre cells a nucleus. The nucleus in each cells contains thousands of genes which are made up from a chemical called DNA. The genes are like codes which control the functions of the cells. For example, different genes control how the cells makes proteins or hormones or others chemicals. Certain genes control when the cells should multiply, and certain genes even control when the cells should die. Most type of cell in the body divide and multiply from time to time as old cells wear out or became damaged. New cells are formed to replace them. Some cells normally multiply quickly. For example you make millions of the (RBC) each day as longs once they are mature-for example brain cells. Normally your body only makes the right numbers of the cells that are needed.

Abnormal cells

Sometimes a cells become abnormal.these occurs because one (or more) gene in the cells becomes damaged or altered. The abnormal cell may then divide in to two.then four,then eight,and so on.lots of abnormal cells may then develop from the original abnormal cell. These cells do not knw when to stop multiplying a group of abnormal cells may then from if this group of cells gets bigger,it becomes a large clump of abnormal cells called a tumor [4-6].

What are tumours

A tumour is a lump or growth of tissue made up from abnormal cells. Tumours are divided into two types: benign and malignant [4-7].

Non-cancerous (benign) tumours

These may form in various parts of the body. Benign tumours grow slowly, and do not spread or invade other tissues. They are not cancerous and are not usually life-threatening. They often do no harm if they are left alone. However, some benign tumours can cause problems. For example, some grow quite large and may cause local

pressure symptoms, or look unsightly. Also, some benign tumours that arise from cells in hormone glands can make too much hormone, which can cause unwanted effects [4-8].

Cancerous (malignant) tumours

Malignant tumours tend to grow quite quickly, and invade into nearby tissues and organs, which can cause damage. Tumours normally develop in one original site - the primary tumour. Malignant tumours may also spread to other parts of the body to form secondary tumours (metastases). This happens if some cells break off from the primary tumour and are carried in the bloodstream or lymph channels to other parts of the body.

These secondary tumours may then grow, invade and damage nearby tissues, and spread again.

Note: not all cancers form solid tumours. For example, in cancer of the blood cells (leukaemia) many abnormal blood cells are made in the bone marrow and circulate in the bloodstream [6, 7].

What are the different stages of Cancer?

The term 'stage of cancer' [6-13] means the stage the cancer was at when it was first diagnosed. Being sure about the stage is very important because it is a critical factor in deciding the best way to treat the cancer. Doctors use a range of ways of describing these stages.

Figure 5: Stages of Cancer cell growth; stage 0 is *in situ* cancer; stage 1 is localized cancer, although further local spread may take it to stage 2; stage 2 also usually includes spread to the nearest lymph nodes; stage 3 usually indicates more extensive lymph node involvement and stage 4 always indicates distant spread.

Stage is also very important to prognosis - prediction of the cancer's effect on the person who has it. On average, the higher the stage, the worse the cancer's effect on the person who has it. The hope of cancer treatment is that it will improve the prognosis, both in prediction and in reality.

A cell that becomes a cancer cell usually does so in the company of other similar cells. Often, but not always, it can produce a tumour right there in that tissue, in a way that poses little or no threat to life. This is called ***in situ* cancer;** that is, cancer in the position where it started. It is probable that some cancers never go beyond this early stage.

At the next stage, the cancer cells gain the ability to pass through the 'basement membrane', that is the thin, fibrous boundary to the tissue in which the cancer began, and to invade neighbouring tissue. This invasion is a serious step, because it indicates that the growing cancer cells may threaten life. While the cancer remains a single lump, partly in the tissue where it began and partly in a neighbouring tissue, it is said to be in the **localised stage**.

Once a cancer cell has invaded, a common next step is for one of its daughter cells to invade through a lymph vessel (a vessel like a blood vessel that carries the clear fluid called lymph, which is all the time exuding into tissue from our blood capillaries (the smallest blood vessels), back to the blood stream). On the way to the blood stream, the cancer cell can get caught in a lymph node, one of the powerhouses of the body's immune system. There it might provoke an immune response against it, which can go on to destroy it and the other cancer cells. Wonderful! Sometimes, though, it divides and forms a lump in the lymph node. This stage is often referred to as **regional spread.** That is, the cancer has spread within the general region in which it first began but not to other parts of the body.

The next step can be quite varied. Cells from the lump in the lymph node may spread further through lymph vessels to more distant lymph nodes or on into the blood stream. Or cells from the original lump may invade a capillary and enter the blood stream that way .Either way, once in the blood stream, the cancer cells can go just about anywhere in the body, form new colonies and spread further. This is the stage of **distant spread [**8-10].

What causes cancer?

Each cancer is thought to first start from one abnormal cell [12]. What seems to happen is that certain vital genes which control how cells divide and multiply are damaged or altered. This makes the cell abnormal. If the abnormal cell survives it may multiply out of control into a cancerous (malignant) tumour.

We all have a risk of developing cancer. Many cancers seem to develop for no apparent reason. However, certain risk factors are known to increase the chance that one or more of your cells will become abnormal and lead to cancer.

Risk factors include the following [10, 12-15]:

Chemical carcinogens

A carcinogen is something (chemical, radiation, etc) that can damage a cell and make it more likely to turn into a cancerous cell. As a general rule, the more the exposure to a carcinogen are the greater the risk of cancer.

Well known examples of carcinogens include:

- **Tobacco smoke**. Smokers are more likely to develop lung cancer, mouth cancer, throat cancer, oesophageal cancer, bladder cancer and pancreatic cancer. Smoking is thought to cause about a quarter of all cancers. About 1 in 10 smokers die from lung cancer. The heavier you smoke, the greater the risk. If you stop smoking, your risk goes down considerably.

- **Workplace chemicals** such as asbestos, benzene, formaldehyde, etc. If you have worked with these without protection you have an increased risk of developing certain cancers. For example, a cancer called mesothelioma is linked to past exposure to asbestos.

Age

The older you become, the more likely you will develop a cancer. This is probably due to an accumulation of damage to cells in the body over time. Also, the body's defences against abnormal cells may become less good as you become older. For example, the ability to repair damaged cells, and the immune system which may destroy abnormal cells, may become less efficient with age. So, eventually one damaged cell may manage to survive and multiply out of control into a cancer. Most cancers develop in older people.

Lifestyle factors

Diet and other lifestyle factors can alter the risk of developing cancer. For example:

- If you eat a lot of fruit and vegetables you have a reduced risk of developing certain cancers. The exact way in which they protect against cancer is not fully understood. These foods are rich in vitamins and minerals, and also contain chemicals called antioxidants. They may protect against damaging chemicals that get into the body. We should all eat at least five portions of fruit and vegetables per day (some experts recommend even more).
- Eating too much fatty food possibly increases the risk of developing certain cancers.
- The risk of developing certain cancers is increased by obesity, lack of regular exercise (physical activity), and drinking a lot of alcohol.

For example, one large research study (cited below) followed up over 55,000 people for 10 years. It looked at lifestyle factors and rates of cancer. The study concluded that by following recommendations on keeping physically active, keeping weight in check, not smoking, drinking alcohol in moderation and having a healthy diet, the risk of developing bowel cancer could be reduced by as much as 23%. But, the study found that even improvement in some of these lifestyle factors had some reduction in risk.

Radiation

Radiation is a carcinogen. For example, exposure to radioactive materials and nuclear fallout can increase the risk of developing cancer of the blood cells (leukaemia) and other cancers. Too much sun exposure and sunburn (radiation from UVA and UVB) increase the risk of developing skin cancer. But note: the risk from small doses such as from a single X-ray test, is very small.

Infection

Some viruses are linked to certain cancers. For example, people with persistent infection with the hepatitis B virus or the hepatitis C virus have an increased risk of developing cancer of the liver. Another example is the link between the human papillomavirus (HPV) and cervical cancer. Most (possibly all) women who develop cervical cancer have been infected with a strain (subtype) of HPV at some point in their lives. However, most viruses and viral infections are not linked to cancer.

Immune system

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

Your genetic 'makeup'

Some cancers have a strong genetic link. For example, in certain childhood cancers the abnormal gene or genes that may trigger a cell to become abnormal and cancerous (malignant) are inherited. Other types of cancer may have some genetic factor which is less clear-cut. It may be that in some people their genetic 'makeup' means that they are less resistant to the effect of carcinogens or other factors such as diet.

Most cancers are probably due to a combination of factors[12-16]

Not everybody who comes into contact with a carcinogen or has an unhealthy lifestyle will develop cancer. For example, not all smokers develop cancer of the lung. In fact, we are all probably exposed to low doses of carcinogens a lot of the time.

The body has certain mechanisms that may protect us from developing cancer. For example, it is thought that many cells that are damaged by carcinogens can repair themselves. Also, the body's immune system may be able to destroy some types of abnormal cells before they multiply into a tumour. Perhaps one carcinogen may only damage one gene, and two or more genes may need to be damaged or altered to trigger the cells to multiply out of control.

In many cases it is likely that a combination of factors such as genetic make-up, exposure to a carcinogen, age, diet, the state of your immune system, etc, plays a part to trigger a cell to become abnormal, and allow it to multiply out of control into a cancer.

Cancer Chemotherapy

Chemotherapy drugs are sometimes feared because of a patient's concern about toxic effects. Their role is to slow and hopefully halt the growth and spread of a cancer. There are three goals associated with the use of the most commonly-used anticancer agents.

1. Damage the DNA of the affected cancer cells.
2. Inhibit the synthesis of new DNA strands to stop the cell from replicating, because the replication of the cell is what allows the tumour to grow.

3. Stop mitosis or the actual splitting of the original cell into two new cells. Stopping mitosis stops cell division (replication) of the cancer and may ultimately halt the progression of the cancer.

Unfortunately, the majority of drugs currently on the market are not specific, which leads to the many common side effects associated with cancer chemotherapy. Because the common approach of all chemotherapy is to decrease the growth rate (cell division) of the cancer cells, the side effects are seen in bodily systems that naturally have a rapid turnover of cells iincluding skin, hair, gastrointestinal, and bone marrow. These healthy, normal cells, also end up damaged by the chemotherapy program.

Categories of Chemotherapy Drugs:

In general, chemotherapy agents can be divided into three main categories based on their mechanism of action.

Stop the synthesis of pre DNA molecule building blocks [16-18]:

These agents work in a number of different ways. DNA building blocks are folic acid, heterocyclic bases, and nucleotides, which are made naturally within cells. All of these agents work to block some step in the formation of nucleotides or deoxyribonucleotides (necessary for making DNA). When these steps are blocked, the nucleotides, which are the building blocks of DNA and RNA, can not be synthesized. Thus the cells can not replicate because they can not make DNA without the nucleotides.
Examples of drugs in this class include 1) methotrexate (Abitrexate),2) fluorouracil (Adrucil), 3) hydroxyurea (Hydrea), and 4) mercaptopurine (Purinethol).

Directly damage the DNA in the nucleus of the cell:

These agents chemically damage DNA and RNA. They disrupt replication of the DNA and either totally halt replication or cause the manufacture of nonsense DNA or RNA (i.e. the new DNA or RNA does not code for anything useful).

Examples of drugs in this class include cisplatin (Platinol) and 7) antibiotics - daunorubicin (Cerubidine), doxorubicin (Adriamycin), and etoposide (VePesid).

Effect the synthesis or breakdown of the mitotic spindles:

Mitotic spindles serve as molecular railroads with "North and South Poles" in the cell when a cell starts to divide itself into two new cells. These spindles are very important because they help to split the newly copied DNA such that a copy goes to each of the two new cells during cell division. These drugs disrupt the formation of these spindles and therefore interrupt cell division.
Examples of drugs in this class of 8) miotic disrupters include: Vinblastine (Velban), Vincristine (Oncovin) and Pacitaxel (Taxol).

1) Methotrexate:

Methotrexate inhibits folic acid reductase which is responsible for the conversion of folic acid to tetrahydrofolic acid. At two stages in the biosynthesis of purines (adenine and guanine) and at one stage in the synthesis of pyrimidines (thymine, cytosine, and uracil), one-carbon transfer reactions occur which require specific coenzymes synthesized in the cell from tetrahydrofolic acid.
Tetrahydrofolic acid itself is synthesized in the cell from folic acid with the help of an enzyme, folic acid reductase. Methotrexate looks a lot like folic acid to the enzyme, so it binds to it thinking that it is folic acid. In fact, methotrexate looks so good to the enzyme that it binds to it quite strongly and inhibits the enzyme. Thus, DNA synthesis cannot proceed because the coenzymes needed for one-carbon transfer reactions are not produced from tetrahydrofolic acid because there is no tetrahydrofolic acid. Again, without DNA, no cell division.

2) 5-Fluorouracil:

5-Fluorouracil (5-FU; Adrucil, Fluorouracil, Efudex, Fluoroplex) is an effective pyrimidine antimetabolite. Fluorouracil is synthesized into the nucleotide, 5-fluoro-2-deoxyuridine. This product acts as an antimetabolite by inhibiting the synthesis of 2-deoxythymidine because the carbon - fluorine bond is extremely stable and prevents the addition of a methyl group in the 5-position. The failure to synthesize the thymidine nucleotide results in little or no production of DNA.

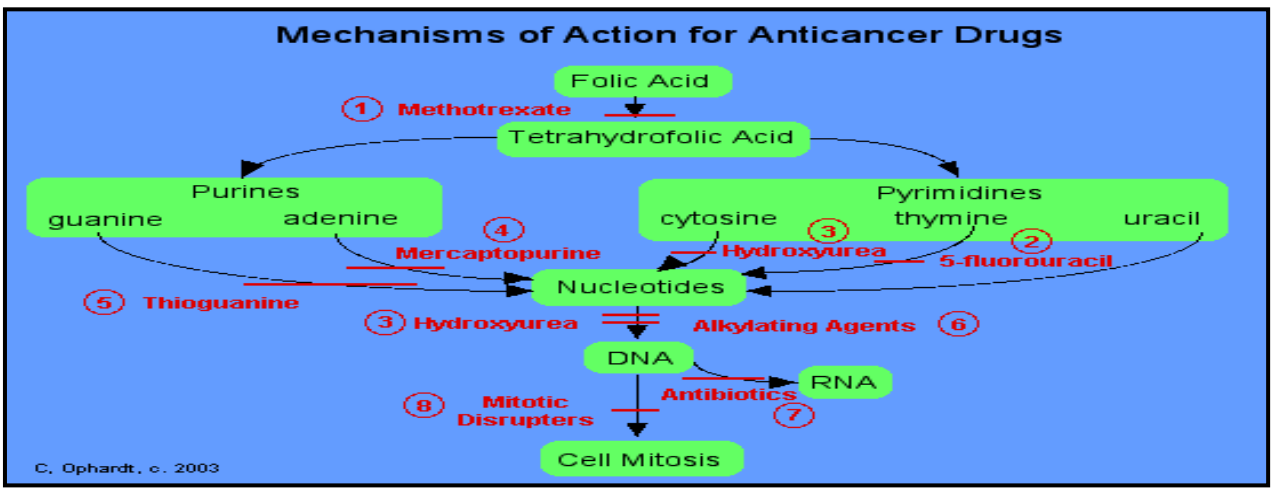

Figure 6: Mechanism of action of anticancer drugs

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Table 1: 5 years survival rate of cancer chemotherapy

Cancer Chemotherapy – 5 years survival rate	
Childhood Acute Lymphoblastic Leukemia	50 - 80%
Acute Adult Lymphoblastic Leukemia	20 - 60%
Childhood Acute Myeloblastic Leukemia	20 - 60%
Adult Acute Myeloblastic Leukemia	10 - 20%
Breast Cancer	5 - 20%
Hodgkin's lymphoma	40 - 80%

Anti cancer

- The anticancer drug either kills cancer cells or modifies their growth.
- Discovery of anticancer agent started after 1940's (when nitrogen mustard was used)
- Most of the agent was discovered in 1950-1970. No treatment before 1940.
- cancer treatment-
- Chemotherapy-After 1965
- Radiotherapy-1955-1965
- Surgery-1955
- Immunotherapy and Gene therapy [13-18].

How is cancer diagnosed?

If a cancer is suspected from your symptoms

Your doctor will examine you to look for abnormalities such as a lump under the skin, or an enlarged liver. You may be referred for tests such as X-rays, scans, blood tests, endoscopy, bronchoscopy, etc, depending on where the suspected cancer is situated. These tests can often find the site of a suspected cancer. However, a sample (biopsy) is often needed to be certain that the abnormality is a cancer and not something else - such as a non-cancerous (benign) tumour [16-20].

Biopsy

A biopsy is a procedure where a small sample of tissue is removed from a part of the body. The sample is then examined under the microscope or tested in other ways to detect abnormal cells. Sometimes it is easy to obtain a biopsy. For example, from a lump on the skin which may be a skin cancer? However, it can be difficult to obtain a biopsy from deeper tissues and it may require specialised procedures [20-22].

What are the treatment options for cancer?

Treatment options vary, depending on the type of cancer and how far it has grown and spread. See the separate leaflets on the specific cancers for more details. There is also another leaflet called Staging and Grading Cancer which discusses how a cancer is classified depending on its type (grading) and how far it has spread in the body (staging). Briefly, the three most common treatments are:

- **Surgery**. It may be possible to cut out a cancerous (malignant) tumour.
- **Chemotherapy**. This is a treatment that uses anti-cancer medicines to kill cancer cells, or to stop them from multiplying. There are various different types of medicines used for chemotherapy. The medicine or combination of medicines selected depends on the type of cancer being treated.
- **Radiotherapy**. This is a treatment that uses high-energy beams of radiation which are focused on cancerous tissue. This kills cancer cells, or stops cancer cells from multiplying.

More recently, other treatments have been introduced which include:

- **Stem cell transplant**. High-dose chemotherapy may damage bone marrow cells and lead to blood problems. However, if you receive healthy bone marrow after the chemotherapy then this helps to overcome this problem.
- **Hormone therapy**. This is the use of medicines to block the effects of hormones. This treatment may be used for cancers that are hormone-sensitive such as some cancers of the breast, prostate and womb (uterus).
- **Immunotherapy**. Some treatments can boost the immune system to help to fight cancer. More specific immunotherapy involves injections of antibodies which aim to attack and destroy certain types of cancer cells. Research is underway to try to find vaccines that would stimulate your own immune system to make antibodies against cancer cells.
- **Gene therapy**. This is a new area of possible treatments. Research is underway to find ways of blocking, repairing or replacing abnormal genes in cancer cells.
- **Special techniques**. These can sometimes be used to cut off the blood supply to tumours. The tumour then dies [16-19].

AVASTIN

Generic name: Bevacizumab
Drug type: Avastin is classified as a "monoclonal antibody" and "anti-angiogenesis" drug.

What is Avastin?

Avastin (bevacizumab) is a cancer medicine that interferes with the growth and spread of cancer cells in the body.
Avastin is used to treat a certain type of brain tumor, and certain types of cancers of the kidney, lung, colon, rectum, cervix, ovary, or fallopian tube.
Avastin is also used to treat cancer of the membrane lining the internal organs in your abdomen. It is usually given as part of a combination of cancer medicines.

Avastin

Avastin [20-25] is given through an infusion into a vein (intravenous, IV). The first dose is given over 90 minutes. The infusion time can eventually be shortened to 30 minutes if well-tolerated.

Factors

Depends on many factors, including height and weight, general health or other health problems, and the type of cancer or condition being treated [19-22].

USES

- Avastin Approved for Late-Stage Cervical Cancer, breast cancer, colon cancer, kindney, lung etc.
- More than 4,000 women projected to die this year from the disease
- Cervical cancer is most often caused by the sexually spread human papillom virus (HPV). More than 12,000 women in the United States will be diagnosed with the disease this year and more than 4,000 women will die from the illness, according to U.S. National cancer Institute statistics.
- Avastin works by interfering with the development of blood vessels that fuel cancerous cell growth. The new approval is for use in combination with other anti-cancer drugs, including paclitaxel, cisplatin and topotecan, the FDA said.
- Avanti's safety and effectiveness in treating cervical cancer were evaluated in clinical studies involving 452 people with persistent, recurring or late-stage disease, the agency said. Average survival among those who took Avastin and chemotherapy drugs was 16.8 months, compared to 12.9 months among those receiving chemotherapy alone [22-25].

Side effects

- Gastrointestinal perforation/ fistula formation/ wound healing complications
- Haemorrhage (severe bleeding)
- Hypertensive crisis (severe high blood pressure)
- Nephrotic Syndrome - a condition marked by very high levels of protein in the urine (proteinuria), low levels of protein in the blood, swelling, especially around the eyes, feet and hands. This syndrome is caused by damage to the glomeruli (tiny blood vessels in the kidney that filter waste and excess water from the blood and send them to the bladder as urine).
- Congestive heart failure in patients who have received prior treatment with anthracycline based chemotherapy, or radiation therapy to the chest wall.
- Most people do not experience all of the side effects listed.
- Side effects are often predictable in terms of their onset and duration.
- Side effects are almost always reversible and will go away after treatment is complete.
- There are many options to help minimize or prevent side effects.
- There is no relationship between the presence or severity of side effects and the effectiveness of the medication.
- There is no data as to the frequency of adverse reactions that may be attributed to avastin alone. (In clinical studies avastin was used in combination with other chemotherapy medications) [20-24].

These side effects are less common side effects (occurring in about 10-29%) of patients receiving avastin

- Shortness of breath
- Dizziness
- High blood pressure
- Weight loss
- Muscle aches and pains

The following side effects are common (occurring in greater than 30%) for patients taking avastin:

- Generalized Weakness
- Pain
- Abdominal pain
- Nausea & vomiting
- Poor appetite
- Constipation
- Upper respiratory infection
- Low white blood cell count. (This can put you at increased risk for infection.)
- Proteinuria (see kidney problems)
- Nose bleed (see bleeding problems)
- Diarrhea
- Hair loss
- Mouth sores
- Headache [23-25]

Prohibited avastin [26-29]

Undergoing surgery:- Avastin should not be used for 28 days before or after surgery and until surgical wounds are fully healed
Pregnant:- Data have shown that Avastin may harm your unborn baby. Use birth control while on Avastin. If you stop Avastin, you should keep using birth control for 6 months before trying to become pregnant
Planning to become pregnant:-Taking Avastin could cause a woman's ovaries to stop working and may impair her ability to have children
Breastfeeding:-Breastfeeding while on Avastin may harm your baby and is therefore not recommended. (25)
Uses
This medication is a man-made antibody (IgG1) used to treat kidney cervical, ovarian, colon, and rectal cancer. Bevacizumab is also used to treat lung cancer (non-small cell type), certain types of brain tumors, and cancer found in the fallopian tube or lining of the abdominal wall (peritoneal). This drug works by blocking a certain protein (vascular endothelial growth factor-VEGF) thereby decreasing the blood supply to the tumor and slowing tumor growth.
Over dose
If overdose is suspected, contact a poison control center or emergency room right away. US residents can call their local poison control center at 1-800-222-1222.

Canada residents can call a provincial poison control center. Symptoms of overdose may include: severe headache [26, 27].

Precautions

- Before using this medication, tell your doctor or pharmacist your medical history, especially of: stomach/intestinal ulcers, bleeding problems (such as recent bloody vomiting or coughing up blood), recent major surgery, recent injuries/wounds, high blood pressure, kidney disease, diabetes.
- Bevacizumab can make you more likely to get infections or may worsen any current infections. Avoid contact with people who have infections that may spread to others (such as chickenpox, measles, flu).
- Do not receive any kind of immunization or vaccination without your doctor's approval while taking avastin.
- Do not breast feed while taking avastin [28-31].

CONCLUSION

Rationally designed drug delivery system enables us to precisely control drug release rates for prolonged duration and sometimes help targeting the drugs such as anti cancer agents to specific body sites. Only in recent years, the idea of development of such systems became practical. In a short time, new drug delivery systems have had an impact on nearly every branch of medicine. With this knowledge, we successfully applied liposome formulation technology for the anticancer drug, Irinotecan. The design and development of liposome formulations posed various challenges involving optimization of drug entrapment, release from the liposome vesicles, stability evaluation, pharmacokinetic and toxicokinetic evaluation and utility as a safer alternative to conventional i.v. administration. The basic idea was to reduce the toxicity of the cytotoxic anticancer drug by making use of relatively low doses and retaining the parent drug in the circulation for longer duration of time, without compromising the clinical efficacy. Liposome formulation demonstrated a great potential in this regard. However, some major issues limiting their utility are short circulation half-life of vesicles, lack of long term stability, batch-to-batch reproducibility, suitable sterilization method, particle size control, and difficulty in large scale production, most of which are acknowledged by our research. These are the problems seem to be limiting the manufacture and development of the liposomes.

The research envisaged in this project, encapsulation of Irinotecan in liposomes employing a lipid hydration procedure resulted in high trapping efficiency and excellent drug retention properties. The flexibility of liposome generation and loading procedure used here has allowed new insights to be gained into various parameters like liposome size, Lipids composition and drugs to lipid ration entraoment efficiency.

Pharmacokinetic and toxicokinetic evaluation along with toxicological assessment is an essential part of development of a novel drug delivery system. The study involved meticulously designed methodology comprised of development and validation of a sensitive, specific, robust bioanalytical method for the determination of Irinotecan and its metabolite, SN-38 by LC- ESI-MS/MS technique, appropriate grouping of animals for pharmacokinetic and toxicokinetic experiments and safety evaluation comprising 132 body weight assessment, diarrhea grading, hematological evaluation, serum biochemistry along with histopatological evaluation. The successful hyphenation of LC and MS has had an enormous impact on the field of quantitative analysis of drugs in biological samples for pharmacokinetic and toxicokinetic evaluation. MS detection provided far better sensitivity and selectivity as compared to other method of detection. Hyphenated Liquid Chromatography and Mass Spectrometry was the most suitable application for identification and quantification of parent drug (Irinotecan) and its metabolite (SN 38) simultaneously.

The LC-MS/MS method developed was simple, robust, specific, selective, sensitive and accurate for Irinotecan and SN-38. It was successfully applied to in vitroand in vivo evaluation of liposome. The assay method found to be suitable for routine analysis of Irinotecan and its metabolite SN-38 in pharmacokinetic and toxicokinetic studies. The simplicity and specificity of the extraction method made it an attractive procedure in high-throughput bioanalysis of Irinotecan.The pharmacokinetic and toxicokinetic evaluation was performed with the help of software, Winnonlin version 5.0.1. This software is the most accepted tool by the industry and regulatory agency for performing pharmacokinetic and toxicokinetic evaluations. The pharmacokinetics of liposomal Irinotecan differed significantly from those of Irinotecan i.v. formulation. The kinetic variables derived from toxicokinetic study correlated with the toxicity findings. The results revealed that the reduction in body weight, reduction in blood counts, severe diarrhea and histopathological changes of selected organs in conventional i.v. formulations were positively correlating predominantly with plasma concentration of SN-38. The same was not observed with liposome formulation.

The study demonstrated that the methodology employed for the formulation of liposome had given promising results in terms of simplicity in preparation, optimum drug entrapment and release, relatively increased stability and yet not contributing to the toxicity. We could demonstrate that our formulation is a promising candidate for further development and clinical utility as the results of in vitro characterization were completely supported by in vivo pharmacokinetic study.

In addition to this to strengthen the argument of safety of formulation, there was a positive correlation between the toxicity observed and toxicokinetic profile when compared with the conventional i.v. formulation. In conclusion, liposome encapsulation of Irinotecan results in a potent drug formulation for the treatment of models of colorectal cancer as a result of increased drug longevity, protection of the active lactone species, maintains an effective plasma concentration and brings significant reduction in toxicity as compared to conventional i.v. formulation. The continuing studies focusing on optimizing the lipid formulation as well as studies with second agents that combine well with

Irinotecan could result in a chemotherapeutic strategy that will improve survival for colorectal cancer patients.

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