THINK INDIA JOURNAL

ISSN:0971-1260
Vol-22-Issue-37-December -2019

A Review on Current Cancer Chemotherapy

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Abstract:

Cancer chemotherapy is getting resistance towards cancer cells and chemotherapy is become failure in the treatment of cancer due to its toxicity and low bioavailability. Scientists are working on treatment of cancer for any alternative methods. There are some alternative methods are available for treatment of cancer other than chemotherapy. Immunotherapy is used to improve the body natural defence mechanism. In immunotherapy the substance was made from our body parts. This therapy useful for the slowing the growth of cells or kills the cancer cells. Another method is stem cell therapy, in which that restores blood-forming stem cells in people who have had demolished by the very high dosages of chemotherapy. Radiotherapy is another method using for the treatment of cancer, which is delivered by linear accelerator. This radiotherapy controls or kill the malignant cells. Surgery is also one alternative method; this method is used to remove the tumor and cancer cells completely out of the body. This surgery method is very effective in the tumor at specific place and the early stage.

1. Introduction:

Cancer is known as group of disease which is involved in the abnormal growth of cell division. Cancer tumors are generally two types, one is malignant tumor and another one is the benign tumor. A malignant tumor are dangerous to the body, due to its metastasis behavior and leave their parental cell and migrate to various sites of the healthy tissues, causes the abnormal growth of cell division and it stops the apoptosis. The primary metastatic cells utilize blood and lymph fluids as vehicles to transfer to the other cells. Metastases are the major cause of mortality and morbidity. Benign tumours will not cause any impairment to the body these can be removed from the body by surgery. Cancer conquers a threat to human health from many years, significant efforts have been performed to develop new approaches for obtaining safe and effective methods for treating disease, which has comprised of searching for more selective and efficient chemotherapeutic agents [1]. Cancer occurs when

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an accumulation of cells displayed uncontrolled proliferation and reaches to distant localities in the body. Surviving chemotherapeutic agents have failed to cross the tumor boundaries and deliver the expected outlines due to resistance generated by them [2].

1.1 Cell cycle

The eukaryotic cell cycle consists four distinct phases such as resting phase (G0) or presynaptic phase (G1), in which phase *de novo* nucleic acid synthesis production occurs. The DNA production occurs in synthetic (S) phase and follows by gap phase (G2). In this phase critical proteins, RNA and mitotic spindle will be formed. Major chemotherapeutic agents are specific for certain phase in the cell cycle [3–5]. These all steps and the proteins involved in the cell cycle was explained in the Figure 1.

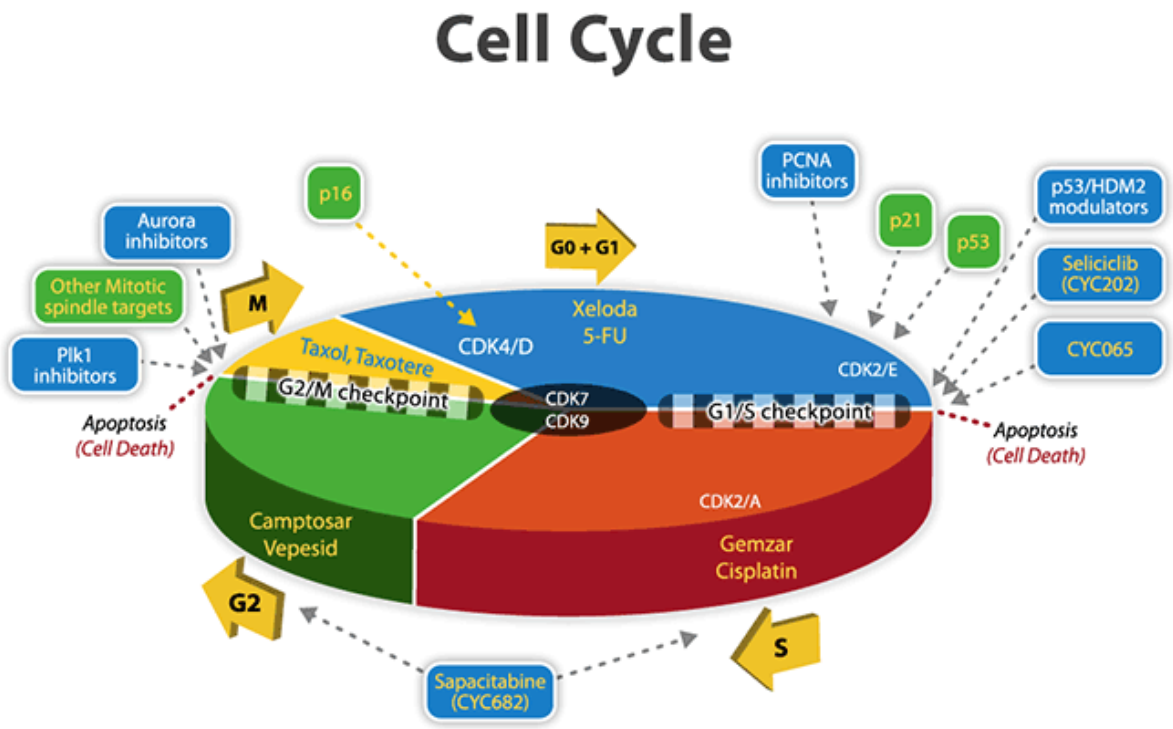

Figure 1: Cell cycle

1.2Causes of cancer:

Cancer can be caused by different types of reasons. Consumption of tobacco, environment polluted chemicals and some industrial smoke that contain several types of carcinogenic chemical compounds that may causes cancer. These carcinogenic agents directly or indirectly

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influence the cytoplasm, nucleic acids that lead to the gene mutations and genetic disorders. When unwanted chemicals enter into the body, chemical changes occur in the cells that lead to the mutations, these mutations cause changes in the cell functions. Some viruses, bacteria's and radiations rays also induce the mutations in the cells that lead to cause cancer. In men, cancer can majorly affect the prostate, lung, bronchus, colon, rectum and urinary bladder respectively. In women, a high prevalence of cancer can be found in the breast, lung, bronchus, colon, rectum, uterine corpus and thyroid respectively [6–10].

1.3 Types of tumors

Cancerous tumor: this type of tumor spread in other parts of the body. Cells can break away and travel through blood or lymphatic system and reaches to lymphatic nodes and other parts. This tumor is also called as malignant.

Non-canceroustumor: this type of tumor are not cenceroustumors so called as no cancerous tumor. This tumor does not spread to the other parts, have covering around itself known as capsule. This can be removed easily out of the body and do not arise again.

Precancerous conditions

Precancerous cells are the abnormal cells which can turn in cancerous cells if not treated on time. If some cells have mild changes, they can be demolish without any treatment but if they get some mutations they can get more abnormal and get proliferate until they become cancer cell.

Based on mild to severe changes precancerous changes can be described as:

Hyperplasia: In this cells are divided at higher rate than that of the normal cells.These cells look similar as normal cell under microscopic studies but the noof cells are higher than normal cells**.**

Atypia: In this type cells are a little abnormal but these cells are benign do not spread anywhere else. These can cause due to healing and inflammation

Metaplasia: this means that there are some mutation in the cells. They look like the same as that of normal cells but they are not the type of normal cells which are found in the tissue. Metaplasia are very rare precancerous.

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Dysplasia: here cells are abnormal and no of cells are higher than that of normal cells. these cells are arranged in irregular manner. Dysplasia is precancerous condition.

Carcinoma in situ: These are highly abnormal cells. This is the severe change in precancerous condition. These are not grown in surrounding tissues but need to be treated immediately as they can readily change into cancer cells.

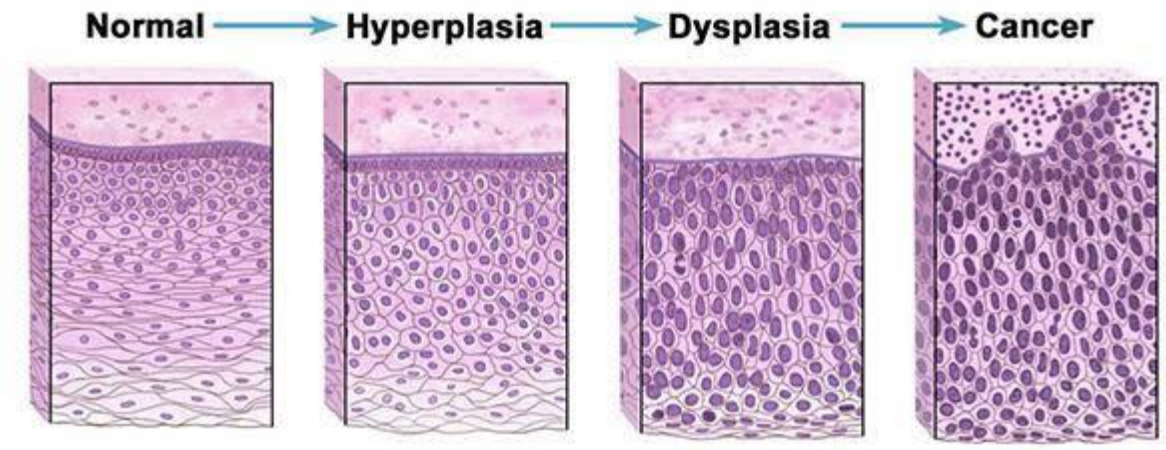
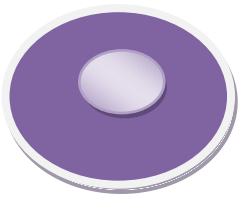
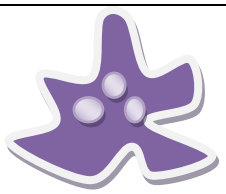


Figure 2: Development of tumor cells

Table 1: Difference Between Cancerous Cells and Non-Cancerous Cells

	Normal cells	**Cancer cells**
		
Shape	Regular	Irregular
Nucleus	Single nucleus	Multi nucleation
Chromatin	Evenly distributed	Aggregated
Growth	Controlled	Uncontrolled

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Maturation	Mature in specialised cells	Remain undifferentiated

2. Chemotherapy

Chemotherapy is a chemical drug therapy which is given to destroy the rapidly growing cells than the normal cells. Chemotherapy is often done in combination with other therapies such as radiation, surgery etc. But this depend uponStage of the disease, previous cancer treatment patient underwent, location of the cancer cells, overall heath.This is called as systemic treatment as the whole body.

2.1Current cancer Chemotherapeutic agents:

Cancers can be treated by different methods like surgery, radiation, with chemotherapeutic agents and some with biological modifiers which stimulates the body immune system by defence mechanism. Cancer chemotherapeutic agents are called antineoplastic agents since they act against new growth. Majorly all these agents interfere with cellular synthesis or function of DNA, RNA and other proteins. Chemotherapy drugs can be classified into several groups based on their mechanism of action in, how they are going to treat the cancer cell. These chemotherapeutic agents can be divided into following groups.

2.1.1**Alkylating agents**

The primary target for alkylating agents is DNA. These can actively divide the DNA molecule, so these agents are also called as DNA cross-linking agents.hese are highly electrophilic in nature and attack the nucleophilic groups on various DNA bases. Thisresults in irreversible alkylation or complexation of the DNA base. The examples are in this class of drugs are mechlorethamine, cyclophosphamide are nitrogen mustards, and Carmustine, lomustine are nitrasoureas, these are bifunctional compounds that one molecule of the drug can bind with the two distinct DNA bases. These agents cross link the DNA at guanine N-7th position and they arrest the cell cycle at late G1 or S phase. Organometallic anticancer agents like Cisplatin and Carboplatin are also cross link the DNA and binds to the adjacent guanine nucleotides [11–14].

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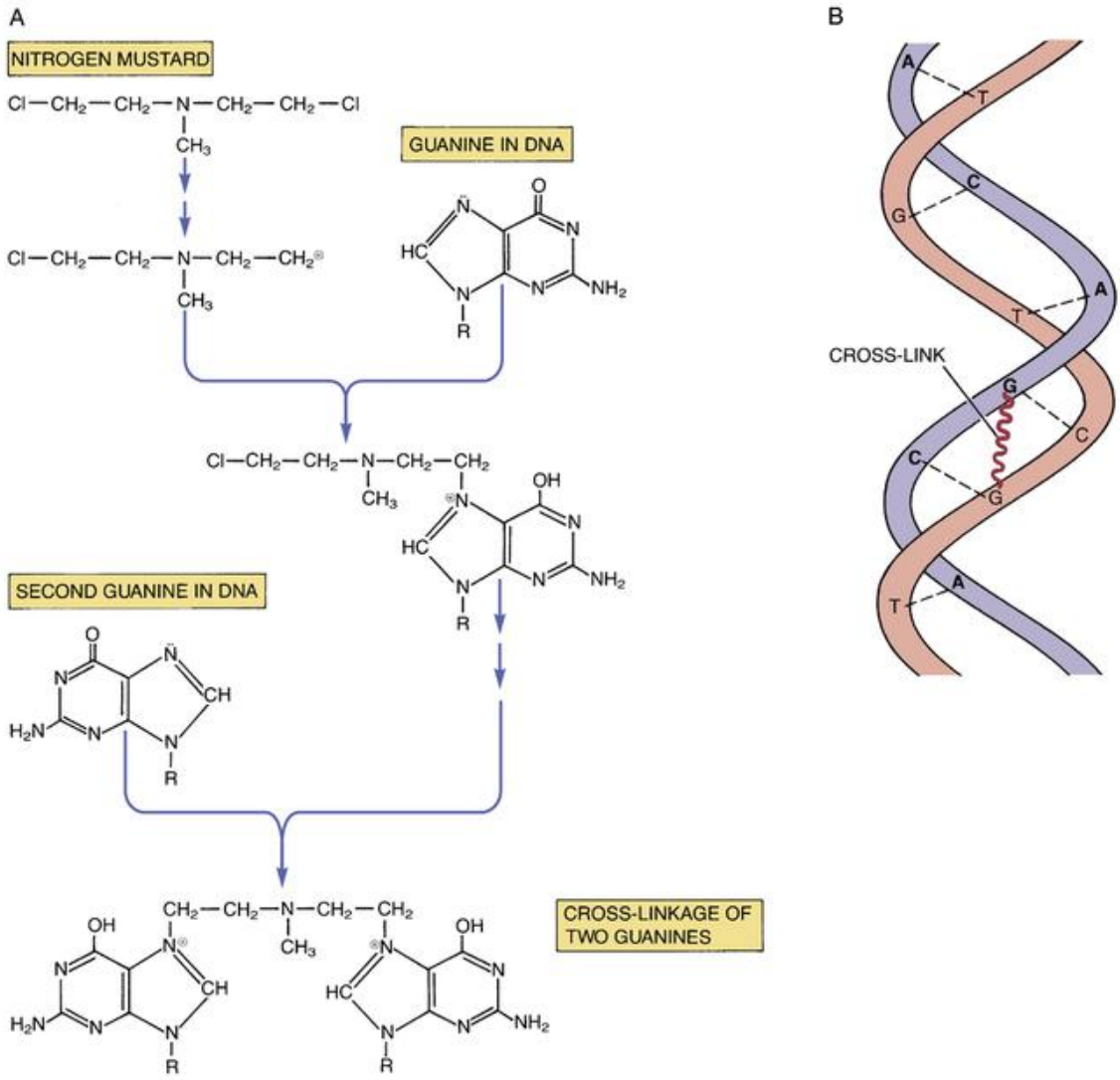

Figure 3: Mechanism of action of alkylating agents.

2.1.2**Anticancer antibiotics**

The anticancer antibiotics are broadly categories into natural and semisynthetic derivatives. These compounds that block the DNA transcription by inducing point mutations in the DNA strand or inhibit the enzymes which are crucial for the DNA replication. These are directly intercalating the DNA base pairs and form the noncovalent interactions with DNA bases. The drugs doxorubicin and daunorubicin are examples of anticancer antibiotics, were shown in They inhibit the topoisomerase II, an enzyme responsible for the proper maintenance of the DNA structure during transcription and replication to RNA. They also showed their cytotoxicity by the generation of free radicals that result breaks the DNA into single strand.

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These anticancer antibiotics major molecular target is DNA, some agents intercalate the DNA and some prevents the DNA repair [15,16].

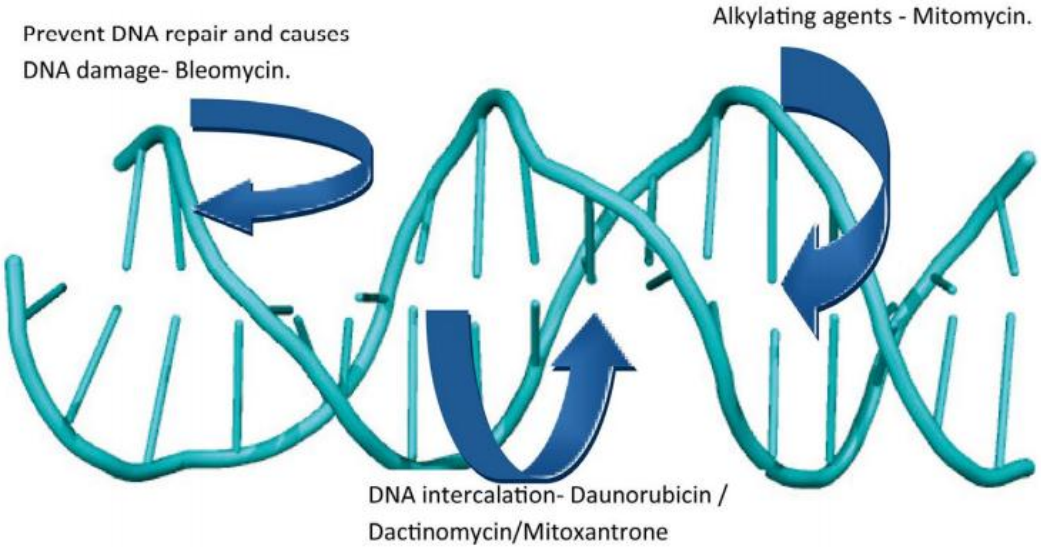

Figure 4: Mechanism of anticancer antibiotics

2.1.3 Antimetabolites

These antimetabolites cause major damage to the DNA and inhibit the ability to replicate. These agents commonly stop the *de novo* DNA synthesis by inhibiting the formation of the nucleotides. Nucleotide biosynthesis is the major target for the antimetabolites because they inhibit the key enzymes which are essential for the synthesis of nucleotides. If the building block nucleotide cannot be synthesized, then automatically tumor growth (DNA synthesis) will be supressed, there by metastasis decelerates and cancer can possibility be cured. Antimetabolites act against the synthesis of metabolites like purines, pyrimidines and folic acid. 5-Flurouracil is used in the treatment of various cancers like colon, breast, anal, rectal and cervical. 6-Mercaptopurine is used for the treatment of acute lymphoblastic leukemia. Methotrexate is used in the treatment of breast, lung and Non- Hodgkin's lymphoma cancers [17–19].

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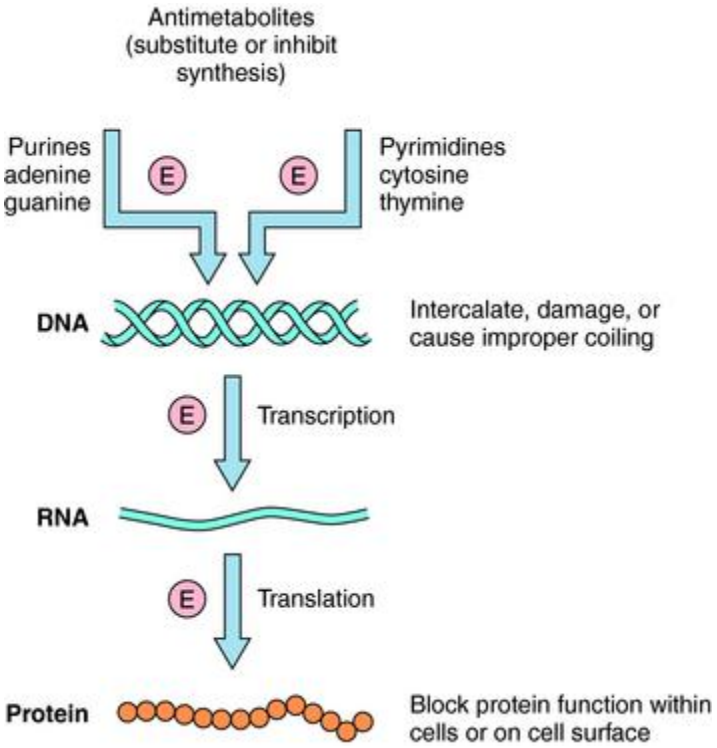

Figure 5: Mechanism of action of Antimetabolites

2.1.4 Topoisomerase Inhibitors:

Topoisomerase is the enzyme which cuts the both strands of the DNA helix and is involved in the formation of DNA duplex that passes through the break. Camptothecin and topotecan are obtained from the plant *Camptothecaacuminata*. These are chiral containing conjugated amino pentacyclic lactones that target the topoisomerase-I and breaks the double strand DNA there by cell death occurs. The epidopodophyllotoxins such as etoposide and teniposide are the semisynthetic glyocosidic derivatives of podophyllotoxins are obtained from the *Podophyllum peltatum*plant also known as American mayapple. Topoisomerase-IIα has two distinct DNA-independent binding sites for the epipodophyllotoxins, one is within the catalytic domain and another one is within the N- terminal ATP binding domain. These topoisomerase inhibitor structures are explained in the. When the toxins bound to the enzyme and stabilize, they form the drug-enzyme-DNA complex, stimulating DNA ligation but inhibiting the resealing. Topoisomerase inhibitors obstructs the activity of topoisomerase enzyme [20–23].

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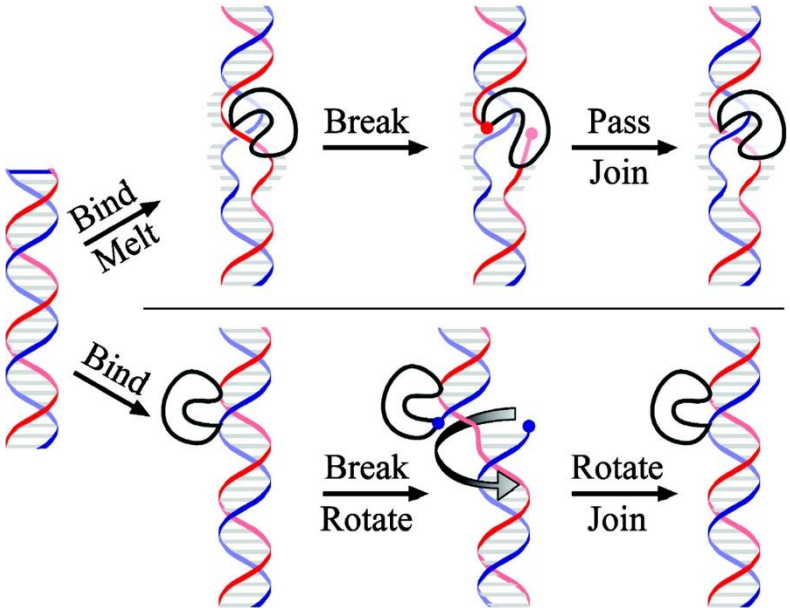

Figure 6: Mechanism of action of topoisomerase inhibitors

2.1.5 Antimitotic agents:

Antimitotic agents have been most successful pharmacological agents for the treatment of cancer. The term "antimitotic agent" has traditionally been synonymous with tubulin targeting compounds. The major antimitotic agents treat the cancer by targeting the tubulin protein an α/β-heterodimer that forms the core of the microtubule. In eukaryotic cell microtubules (MTs) are tubular polymers and they are major cytoskeletal components. The drugs paclitaxel and docetaxel are obtained from the plant *Taxus brevifolia*. These drugs bind to the polymerized β-tubulin at the taxol binding site thereby microtubules resistant to depolymerization and prone to polymerization. This process promotes the elongation phase of microtubule dynamic instability at the expense of shortening mitotic spindle and inhibits the disassembly of tubule into the mitotic spindle. Vinca alkaloids such as vincristine and vinblastine are obtained from the C*atharanthus roseus*. These drugs are having opposite action to the toxoids, these halt the cell division by inhibiting the tubulin polymerization. They bind with both α and β-tubulin then protein-cross linking occurs which promotes a stabilized protofilament structure and disrupts the microtubule depolymerisation. Other drugs, colchicine and nocodazole, are also treating the cancer by targeting the tubulin protein. The dynamic and mutual interconversion of microtubules and tubulins are responsible for the variety of cellular functions such as maintaining the cell structure, providing the intracellular transport for the motor proteins kinesin and dynein are involved in enabling cell division through spindle formation during mitosis, this pulls apart the eukaryotic chromosomes.

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Microtubules (MTs) are the attractive molecular targets in cancer chemotherapy due to their involvement in cellular process. These antimitotic agents not only disturbs the mitosis which are also arrest the cells during interphase. Tubulin has its own different binding sites like taxane/epothilone, vinca alkaloid and colchicine sites. Mitosis inhibitors bind to the tubulin protein and inhibits the mitosis [24–29].

Figure7: different binding sites of tubulin inhibitors

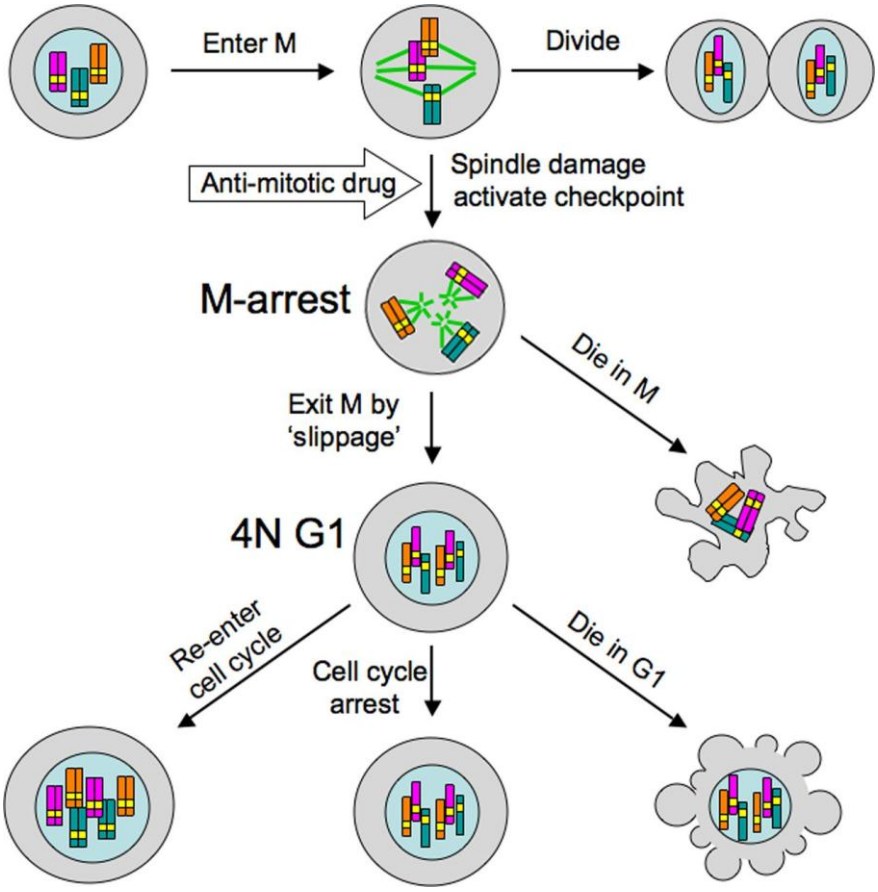

Figure 8: Mechanism of action of Antimitotic drugs

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2.2 Problems occurring with current cancer chemotherapy

As the chemotherapy kills rapidly proliferating cells which are cancer cells, other cells in the body also divide rapidly. Cells in the following area are affected. These chemotherapeutic agents majorly affected places are blood, hair, skin and lining of intestinal tract. Current chemotherapy was suffering from many toxicities that includes easy bruising and excessive bleeding that results in diarrhoea, dry mouth, mouth sores, fatigue, fever, hair loss, loss of appetite, nausea, vomiting, weight loss, pain from nerve damage, infections, anaemia, constipation, neuropathy, lymphedema, memory problems, concentration problems, skin changes, nail changes, insomnia. These all the minor side effects cause while using chemotherapy, these all side effects further leads to causes long lasting toxicity to major organs like heart, kidney, lungs, reproductive system and nervous system [30].

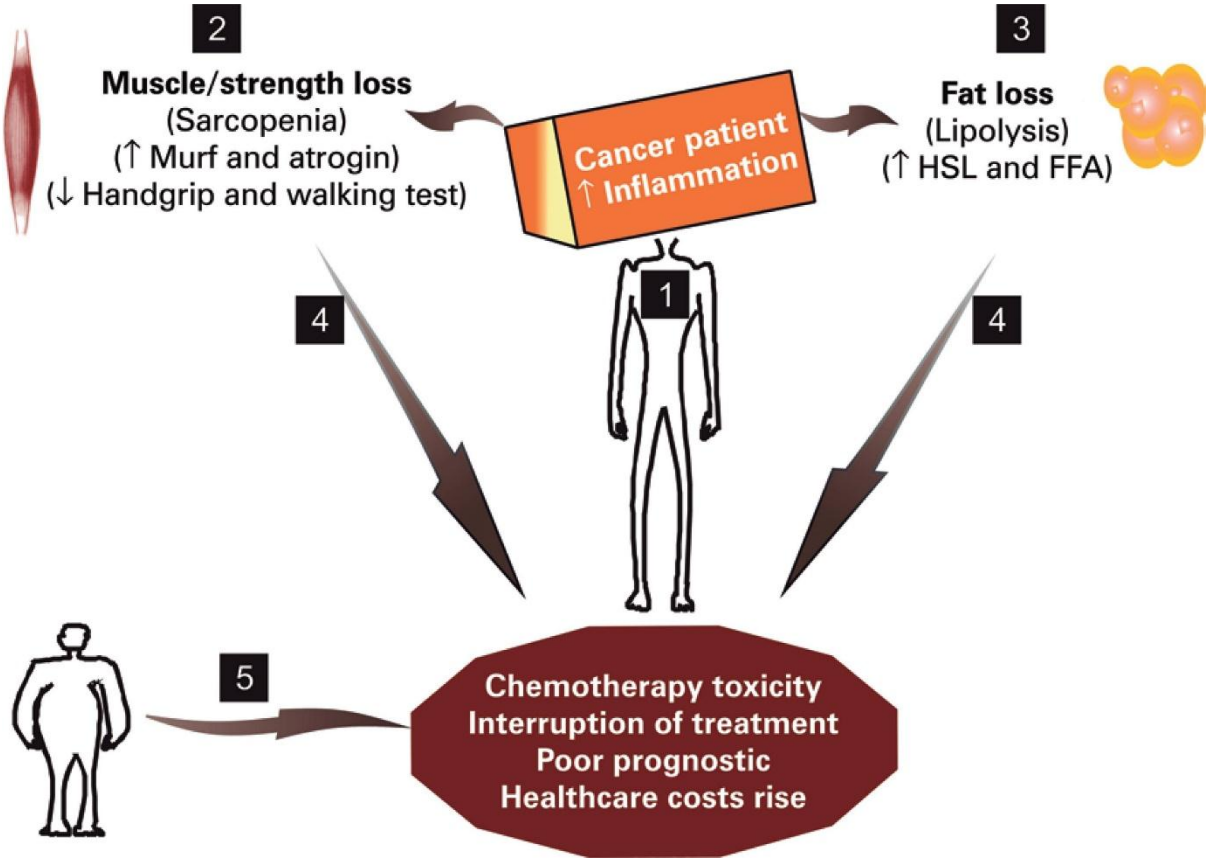

Figure 9: Toxicity of cancer chemotherapy

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2.3 Major failures of cancer chemotherapy:

There are different reasons for the failure of cancer chemotherapy has the ability to become resistant to some drugs, efflux of the drug, increased tolerance to the DNA. By chemotherapy some tumor cells are killed which are drug sensitive but tumor which is resistant to the drug grows again. There are many cases studied which are multidrug resistant, mainly the breast cancer. Mechanism of multidrug resistance are not fully identified which makes the effectiveness therapy difficult. Identification of the mechanism will improve the effect of the treatment. Along with these all problems the above discussed toxicities are also other major reasons for the failure of cancer chemotherapy. Due to these reasons' scientists are searching for alternatives therapies and adjuvant therapies for cancer chemotherapy.

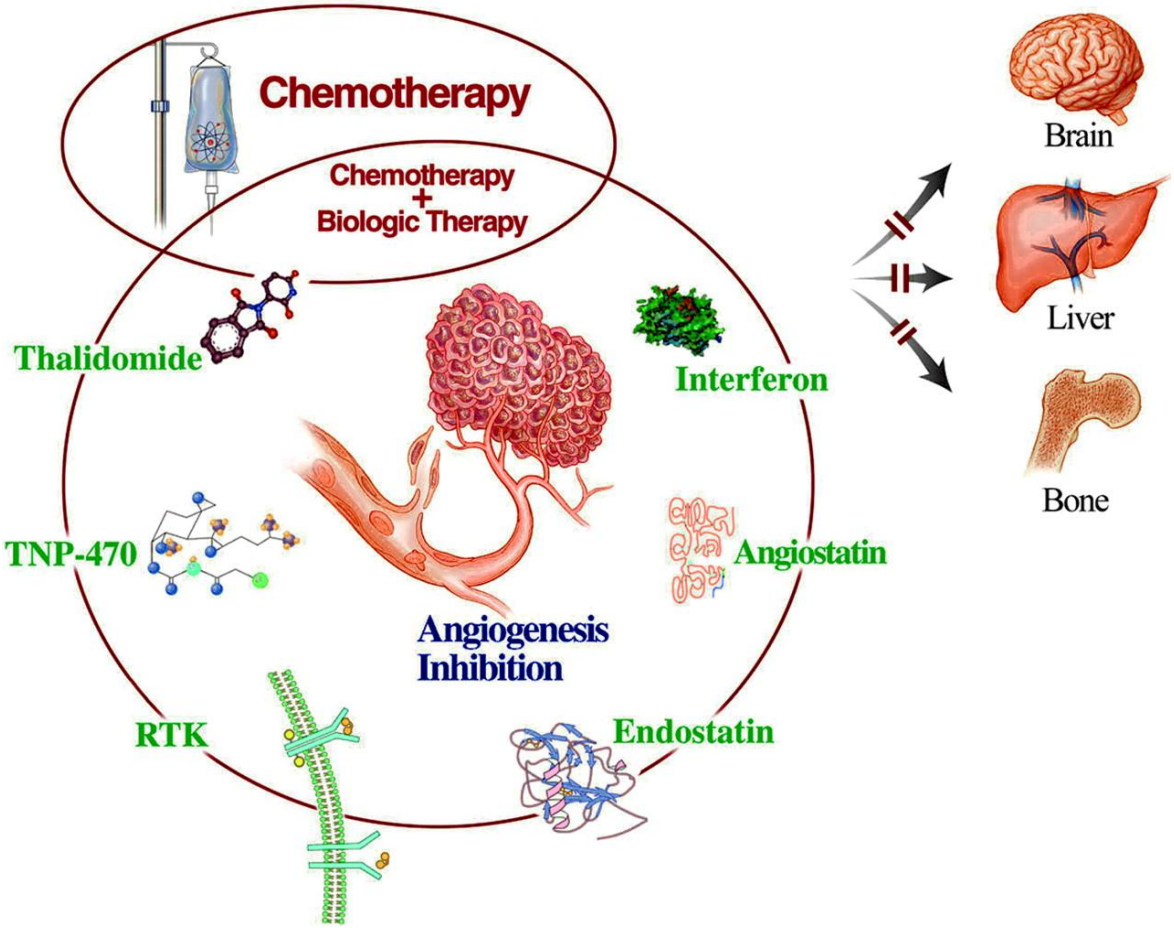

Figure 10: Mechanism of chemotherapy in human body

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