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A Comprehensive Review

Pharmacological Strategies in Cancer Management: A Comprehensive Review

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Abstract:
Cancer is a deadly disease and is the major cause of death worldwide. According to WHO cancer accounts for nearly 10 million deaths in 2020 or about 1in 6 deaths. The impact of factors is widespread, affecting various organs and tissues in the body. The types of cancer such as breast, brain, lung, kidney, colorectal, lymphoma, as well as skin represent a diverse range of malignancies. The risk factors for developing cancer can include genetic factors, environmental exposures (such as tobacco smoke, ultraviolet radiation, and certain chemicals) lifestyle factors (such as diet and physical activity) and infections. The hallmarks of cancer represent a set of characteristics or capabilities that are commonly acquired by cells during the development of cancer. Multidrug resistance in cancerous cells is their ability to withstand the effects of multiple chemotherapeutic drugs, even if these drugs have different structures. The various Nano-drug delivery systems have been explored as a strategy to overcome multidrug resistance in cancer treatment.
Keywords: Cancer, chemotherapy, radiation, biopsy, tumour, gene mutation

Introduction

Cancer is a significant global health concern and a leading cause of death worldwide. Cancer is defined as a complex group of diseases characterized by uncontrolled growth of cell also invade the others parts of body when abnormal cells grow uncontrollably, go beyond their boundaries to effect other parts of the body and spread to other organs. A neoplasm (abnormal mass of tissues) and malignant tumor (cells that can invade nearby tissues and spread to other parts of the body) are the common names of cancer. Annually, 10 million people die due to cancer. Approximately 14, 16,427 cases of cancer were found in India for the year 2022. In India, one in nine people are suffering due to developing cancer in their lifetime. Lung and breast cancers are the leading cause of deaths among other types of cancer. Estimates suggest deaths due to cancer will increase by 12.8% in 2025 as compares to 2020 [1]. According to National Centre for health statistics in 2023, 1,958,310 new cancer cases and 609,820 cancer deaths are estimated to occur in United States. It is the second approximately 9.6 million deaths were estimated to be due to cancer in 2018 [2]. These statistics highlight the substantial burden of cancer related deaths. Recent data identified cancer as the second leading cause of death globally. [WHO 2022] This underscores the importance of addressing cancer [3].

Prevention, early detection, and effective treatment strategies to reduce its impact on public health. International collaboration and support are crucial to developing effective

strategies to reduce the impact of cancer on global health. Treatment approaches for cancer can include surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy among others [4]. Early detection and advances in cancer research and treatment have improved outcomes for many cancer patients, but the disease remains a significant global health challenge. Regular screenings, lifestyle choices, and awareness can contribute to prevention and early detection of cancer [5].

History of Causes of Cancer

A Global Perspective' is a report which is published by the World Cancer Fund and the American Institute for Research on Cancer, which provides an analysis of natural agents that cause cancer, illustrated in Figure 1 [6-8].

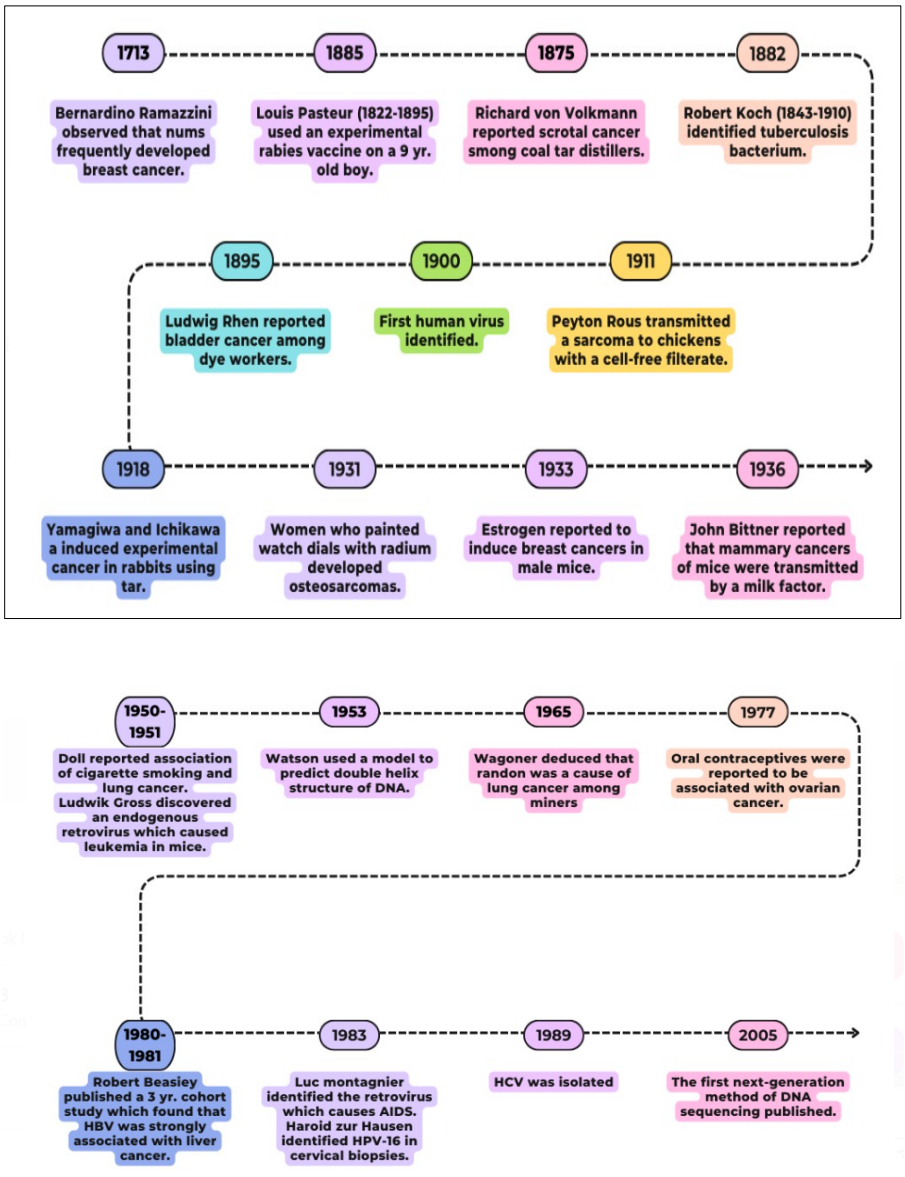

Figure:1 History of Causing agents of cancer [6-8]

Causes of Cancer

Cancer is one of the leading causes of death worldwide and is considered a major public health problem. It develops when normal cells in the body undergo genetic changes (mutations) that cause them to grow and divide uncontrollably [4]. Normally, the body regulates cell growth through a controlled process of cell division and cell death. However, when DNA is damaged and not properly repaired, abnormal cells continue to multiply, forming tumours and sometimes spreading to other parts of the body through metastasis. Cancer does not usually result from a single cause; rather, it develops due to a combination of lifestyle, environmental, infectious, and genetic factors over time [8].

One of the most significant causes of cancer is tobacco consumption. Tobacco use accounts for approximately 22% of cancer-related deaths globally. Tobacco smoke contains numerous harmful chemicals that damage DNA and interfere with the body's natural repair mechanisms. Smoking is strongly associated with cancers of the lung, mouth, throat, oesophagus, pancreas, bladder, and kidney [6]. In addition to smoking, smokeless tobacco products and exposure to second-hand smoke also increase the risk of cancer. Because tobacco-related cancers are largely preventable, reducing tobacco use remains one of the most effective cancer prevention strategies [7].

Lifestyle-related factors such as excessive alcohol consumption, poor diet, obesity, and lack of physical activity contribute to nearly 10% of cancer deaths worldwide. Alcohol increases the risk of cancers of the liver, breast, oesophagus, and colon. It can damage body tissues and produce harmful substances that promote cancer development. Obesity and physical inactivity are also major risk factors for several cancers, including breast, colorectal, endometrial, and kidney cancers [8]. A diet high in processed foods, red meat, and unhealthy fats, combined with low intake of fruits and vegetables, further increases cancer risk. Maintaining a healthy weight, engaging in regular physical activity, and consuming a balanced diet can significantly reduce the likelihood of developing cancer [9].

Infections are responsible for approximately 15% of cancers globally. Certain viruses, bacteria, and parasites can cause chronic inflammation or directly damage DNA, leading to cancer. For example, chronic infection with the Hepatitis B virus and Hepatitis C virus can lead to long-term liver inflammation and eventually liver cancer [10]. Infection with Human papillomavirus is a major cause of cervical cancer and is also linked to anal, throat, and penile cancers. The bacterium Helicobacter pylori can infect the stomach lining and increase the risk of stomach cancer. Human immunodeficiency virus weakens the immune system, reducing the body's ability to fight cancer cells and increasing the risk of certain cancers. Another virus, Epstein–Barr virus, is associated with lymphomas and nasopharyngeal cancer [11]. Preventive measures such as vaccination, early detection, and proper treatment of infections can significantly lower cancer risk [12].

Cancer-causing agents are known as carcinogens and are generally classified into three main categories: physical, chemical, and biological carcinogens [13]. Physical carcinogens include different types of radiation, such as ultraviolet (UV) radiation from sunlight and ionising radiation like X-rays, gamma rays, alpha particles, beta particles, radon, and uranium. These forms of radiation can damage DNA and cause mutations that may lead to cancer, particularly skin cancer and leukaemia [14-22]. Chemical carcinogens include harmful substances such as benzene, vinyl chloride, nickel compounds, arsenic in contaminated

drinking water, and aflatoxins found in contaminated food. Long-term exposure to these chemicals increases the risk of various cancers by altering normal cellular processes [15]. Biological carcinogens include certain viruses, bacteria, and parasites that promote cancer development through chronic infection and inflammation [16].

Although most cancers are caused by environmental and lifestyle factors, approximately 5–10% of cancers are due to inherited genetic mutations passed down from parents. Some individuals inherit defective genes that reduce the body's ability to repair damaged DNA or control cell growth. For example, mutations in the BRCA1 and BRCA2 genes significantly increase the risk of breast and ovarian cancers [17]. These genes normally function as tumour suppressor genes, helping to repair DNA damage. When they are mutated, the risk of uncontrolled cell growth increases. Individuals with a strong family history of certain cancers may benefit from genetic counselling and testing to assess their risk [18].

Cancer is a complex disease caused by multiple interacting factors, including tobacco use, alcohol consumption, poor diet, obesity, lack of physical activity, infections, radiation exposure, chemical substances, and inherited genetic mutations [19]. While some risk factors, such as inherited genes cannot be changed, many causes of cancer are preventable [20]. Adopting a healthy lifestyle, avoiding tobacco and excessive alcohol, maintaining a balanced diet, staying physically active, protecting against infections, and minimising exposure to carcinogens can significantly reduce the global burden of cancer [21].

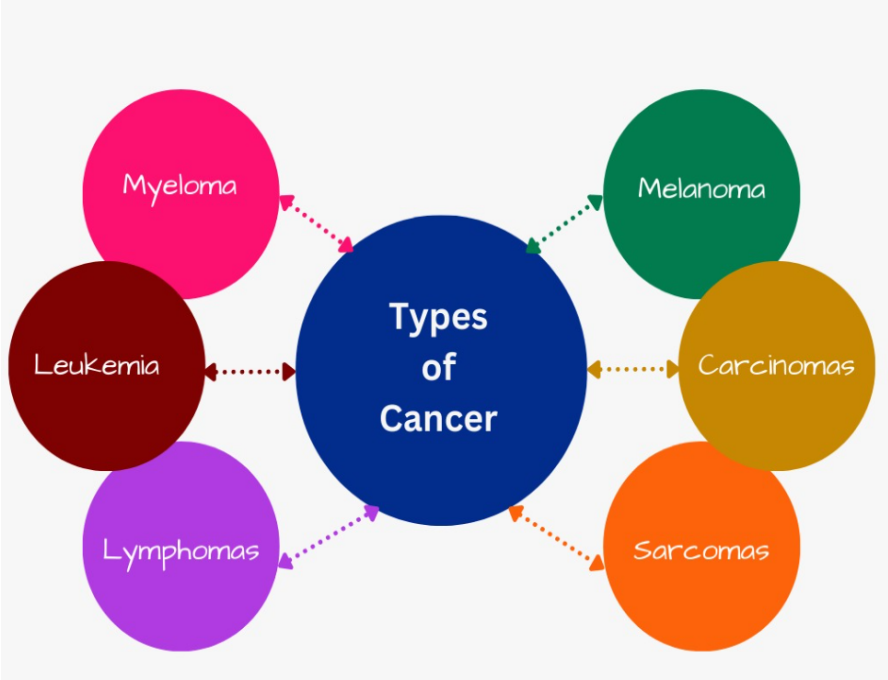

Figure 2: Different types of cancer [14-22]

Hallmarks of Cancer: The Next Generation

Four hallmarks of cancer represent set of distinctive and complementary capabilities that are acquired during cancerous cells growth and metastatic dissemination [22]. They include

Sustaining proliferative signalling: Normal cells need growth signals to enter into an active proliferative state through trans membrane receptors that bind to a particular class of signalling molecules from a quiescent state. [23-25]. Tumour cells can generate their own signals and therewith reducing their dependence on external stimulation factors from their normal tissues environment by altering extracellular growth signals, by altering intracellular circuits that translate those signals into actions. [26].

Evading growth suppressors: Growth suppressors are the "turning off" of cell division. The two common tumor suppressor genes are p53 proteins and retinoblastoma (RB) associated proteins. Mutations in these genes results in the uncontrolled growth of cell and tumor formation.

Resisting cell death: Normal cells die due to programmed cell death called apoptosis whereas cancerous cells are resist of cell death and continue to accumulate in the body by various mechanisms such as loss of p53 tumor suppressor function, by increasing the expression of (Bcl-2, Bcl-XL Mcl-1) ant apoptotic regulators, by down regulating (Bax, Bim, Apaf-1) the proapoptotic Bcl-2-related factors, radiotherapy , nutrient starvation, and certain toxic drugs to induce elevated levels of autophagy that evidently protect cancer cells via resistance to apoptosis [27-28].

Enabling replicative immortality, including angiogenesis, and activating invasion and metastasis- Loss of telomere enable the cell to divide and undergo p53 dependent cell cycle arrest, cancer cells instead activate the telomerase enzyme which maintain the telomere length and cells become immortal [29]. Angiogenesis is the process of formation of new blood vessels out of pre- existing capillaries necessary for the blood supply to the tumou cells if they grow beyond a few mm in size [30]. Invasion refers to the mechanism of invading surrounding cells and metastasis is the process by which tumor cells migrate from primary tumour to new location and establish a new tumor in the new environment [31].

Diagnosis and Treatment of Cancer

The diagnosis of cancer typically involves a combination of medical history review, various diagnostic tests and physical examination. Some of the common methods used for the diagnosis of cancerous cells [32].

Biopsy: the removal of a small sample of tissue from the suspected tumour, which is then examined under a microscope by a pathologist [33]. Different types of biopsies include fine-needle aspiration, core biopsy, or surgical biopsy.

Imaging tests: Imaging techniques such as CT scans, X-rays, MRI, ultrasound, and PET scans are used to visualize the internal structures of the body and identify the presence of abnormal masses or tumors [34].

Endoscopy: It involves using a thin flexible tube with a camera to visualize the inside the organs or body cavities. It can be used to detect the abnormalities and obtain tissues samples.

Blood tests: Blood tests may have conducted to detect specific markers associated with certain types of cancer. For example, (PSA) prostate-specific antigen for prostate cancer, or for ovarian cancer CA-125 [35].

Genetic testing: Genetic tests can identify specific mutations under a microscope. Pap smear test for cervical cancer and sputum cytology for lung cancer are examples of cytological tests [36].

Tumour markers: Some cancers produce substances that can be detected in the blood. Tumor marker tests measure these substances. Some cancer markers are Alpha-fetoprotein

(AFP) for liver and germ cell tumors, B-cell immunoglobin rearrangement for lymphoma leukemia, BCL2 gene for lymphomas and leukemia, B2M for multiple myeloma, chromic lymphatic leukemia and some lymphomas, BRCA1 and BRCA2 for ovarian and breast cancer, BRAF 600 mutations for cutaneous melanoma, colorectal cancer, and lung cancer and many more [37].

Once the diagnosis is confirmed, further tests may be done to determine the extent of the cancer, which helps in treatment. Along with the cancerous cells the normal cell gets damaged due to the treatment. Common side effects are shown below [38].

Anemia

Appetite loss

Bruising or bleeding

Constipation

Diarrhea

Edema

Fatigue

Fertility issues in both men and women

Hair loss

Infection and Neutropenia

Lymphedema

Concentration or Memory problems

Mouth and throat problems

Nausea and vomiting

Nerve problems

Organ related inflammation

Pain and Sexual health issues

Treatments for cancer:

Surgery:

Surgery is one of the primary treatment options for various types of the cancers to prevent the spread of tumor by removing the lymph nodes with the help of scalpels to cut through muscles, skin and sometimes bone [39-40]. It is used for the solid tumor and only used for benign cancer [41]. Several surgeries do not involve any cut which are Cryosurgery (treatment of the cancerous cells of cervix and skin with the help of argon and nitrogen gas), Laser (powerful beam of light is used for of internal organs such as vagina, cervix and is widely used because of its focus on small areas), Hyperthermia (the affected part is exposed to high temperature to destroy cancerous cells), Photodynamic Therapy (drugs are used for cancer treatment) [42].

Chemotherapy:

It is a type of cancer treatment drugs are used to kill or slow the growth of cancerous cells or also by shrink tumors that causing pain in different ways such as oral, intravenous, intramuscular, intra- arterial. Chemotherapeutic drugs are work by targeting rapidly dividing cells, which is a characteristic of most of cancer cells. Drugs used in chemotherapy depends on the type of cancer

Example- Neoadjuvant chemotherapy (tumor is made small before surgery), Adjuvant

chemotherapy (cancer cells are destroyed that remains after treatment).

Immunotherapy:

It is known as biologic therapy and biotherapy, is a cancer treatment that may activates the body's own immune system to recognize and destroy cancer cells. The immune system includes thymus, spleen, lymph node, bone marrow, and skin to fight against pathogen [43]. Immunotherapies boost the body's immune response towards pathogen. These therapies are given by various ways like through pills, intravenously etc.

Targeted Therapy:

In this type of treatment, the targeted cancerous cells are affected while minimizing the damage to normal cells. This approach is based on the understanding of the molecular and genetic changes that drive the development and progression of cancer. Some common types of targeted therapies are monoclonal antibodies, tyrosine kinase inhibitor, proteasome inhibitors, PARP inhibitors, hormone therapy, and angiogenesis inhibitors [44]. Targeted therapy are often used with other cancer treatments such as chemotherapy, surgery, and radiation therapy. Resistance to targeted therapy can develop over time, leading to the need for ongoing research and the development of new treatment strategies [45]. Targeted therapy along with immune system help to mark the cancer cells so that immune system can easily recognize and destroys cancerous cells. It stops the growth of the cancer cells by interfering with proteins that carry the signal on its surface and preventing them from telling the cells to divide.

Stem Cell Transplant:

Stem cell transplant is a medical approach used for the treatment of certain types of cancer, particularly blood- related cancers such as lymphoma, leukemia, and multiple myeloma. The procedure is not used to transplant cancer but rather to treat cancer cells [46]. Some types of stem cell transplantation are 1) Autologous stem cell transplantation (patient own stem cells are collected from their bone marrow), 2) Allogenic stem cell transplantation (stem cells are obtained from donor, who is often close genetic match or unrelated donor), 3) Cord blood transplantation (Stem cells are obtained from umbilical cord blood of newborns, which is rich in hematopoietic stem cells. These stem cells are stored in cord blood banks and can be used for transplantation. Stem cell transplantation helps to replace or repair damaged bone marrow and blood cells, especially after intensive treatments that may damage the patient's own bone marrow [47].

Drugs used in cancer treatment

Precision medicine involves identifying specific genetic or molecular features of a patient's tumor to guide the selection of targeted therapies [48]. The process by which new blood vessels form from pre-existing vessels. Angiogenesis is essential for tumour growth and metastasis because tumours require a blood supply for oxygen and nutrients.

Drugs such as Angiostatin K13 and Endostatin act as natural angiogenesis inhibitors by suppressing endothelial cell proliferation and tumour progression. Fumagillin directly inhibits endothelial cell growth, thereby preventing new blood vessel formation, tabulated in Table No. 1,2,3. Minocycline downregulates the transcription of genes involved in angiogenesis, reducing vascular development at the molecular level. Staurosporine also suppresses endothelial cell proliferation and angiogenic activity.[18] Overall, these drugs limit tumour expansion by targeting the vascular support system required for cancer progression. These drugs interfere with DNA structure and function, leading to inhibition of replication and induction of cell death [10].

Carboplatin forms DNA adducts that trigger apoptosis. Carmustine acts as a DNA alkylating agent and is particularly effective against gliomas and other solid tumours. Cyclophosphamide crosslinks DNA strands,

resulting in strand breakage and impaired replication. Melphalan forms intrastrand crosslinks within DNA, disrupting its normal function. Mitoxantrone intercalates between DNA base pairs, thereby inhibiting DNA synthesis and cell division [40].

Mitomycin C inhibits nuclear division and DNA synthesis, suppressing cancer cell proliferation. Methotrexate blocks thymidine biosynthesis by inhibiting dihydrofolate reductase, which is essential for DNA replication. 5-Fluorouracil inhibits thymidylate synthase, thereby preventing thymidine formation and DNA synthesis [18]. Ganciclovir induces apoptosis by interfering with viral DNA polymerase in infected cells. Hydroxyurea inhibits ribonucleotide reductase, blocking the synthesis of deoxynucleotides required for DNA replication.

Table 1: Effects of drugs on Angiogenesis [40,41,48]

DRUGS	EFFECTS OF DRUGS
Angiostatin K13	Inhibits the angiogenesis and endothelial cell growth
Endostatin	Inhibitor of cell proliferation and tumor growth.
Fumagillin	Inhibits angiogenesis and endothelial cell proliferation
Minocycline	Down regulates the transcription off genes in angiogenesis.
Staurosporine	Inhibit angiogenesis and endothelial cell proliferation.

Table 2: Effects of drugs on DNA binding grooves [40, 41,48]

Name	Mode of Action
Carboplatin	Forms DNA adduct and induce apoptosis
Carmustine	DNA alkylating agent effect against other solid tumors glioma.
Cyclophosphamide	Crosslinks DNA and causes strand breakage.
Melphalan	Forms DNA intrastrand crosslinks.
Mitoxantrone	Inhibit synthesis of DNA by intercalating DNA

Table 3: Effects of drugs on DNA synthesis [40, 41,48]

Name	Mode of Action
Mitomycin C	Inhibitor of, nuclear division, DNA synthesis, and proliferation of cancer cells.
Methotrexate	Block thymidine biosynthesis.
5- Fluorouracil	Inhibits thymidylate synthetase
Ganciclovir	Cause apoptosis
Hydroxyurea	Block the synthesis of deoxynucleotides by inactivating ribonucleoside reductase.

Table 4: Effects of drugs on Transcription regulators

Name	Mode of Action
Actinomycin D	Inhibit cell proliferation and block mRNA production.
Daunorubicin	Complexes to DNA and blocks RNA polymerase to produce mRNA.
Doxorubicin	Inhibits reverse transcriptase and RNA polymerase by binding to DNA.
Homoharringtonine	Binds to 80S ribosome and inhibit protein synthesis.
Idarubicin	Antileukemia agent with higher DNA binding capacity and greater Cytotoxicity.

MDR Resistance in Cancer

The Phenomenon of resistance to multiple drugs having different chemical structures and their targets poses a serious challenge to the success of chemotherapy. MDR can be defined as a type of acquired resistance in microorganism and cancer cells against chemotherapeutic drugs with diverse chemical compositions and mechanisms of action [44]. Multidrug resistance is the biggest concerns in the treatment of cancer by chemotherapy, although some mechanisms behind MDR and methods to assess it have been discovered, there is still a need for comprehensive understanding of these aspects [45]. Multidrug resistance in cancer cells can arise from different factors like epigenetic alterations, increase in DNA repair capacity, genetic mutations, gene amplifications elevated metabolism of xenobiotic substances and high efflux of drugs. These are the mechanisms that contribute to a decrease in the therapeutic effectiveness of drugs making cancer treatment extremely challenging [46].

Mechanisms of MDR Resistance

Increase in DNA Repair Capacity:

Chemotherapeutic drugs like 5- fluorouracil (5-FU) and cisplatin eliminate cancer cells by causing DNA damage. The DNA damage response initiated by the targeted cell in response to this therapeutics can reduce the effectiveness due to the repair of DNA lesions, which further results in the development of drugs. The use of DNA repair pathway inhibitors with DNA damaging chemotherapeutic drugs can demonstrate effectiveness. Also, changes in DNA repair pathways that occur during tumor development can make cancer cells dependent on limited DNA repair mechanisms for survival [47]. Evidence suggests that drugs inhibiting one of these pathways in tumors can be valuable for therapies.

Efflux of Drugs:

Increase in efflux of chemotherapeutics results in reduced accumulation of drugs inside the cells and is recognized as a significant factor contributing to resistance in chemotherapy [48]. The resistance due to high rate of efflux can be intrinsic if exists before drug administration or acquired if develops after the administration of drugs. An example of proteins responsible for increased efflux of drugs are the ABC (ATP-binning cassette) family proteins located in the cell membrane [49]. They constitute the largest family of trans membrane proteins, classified into eight subfamilies A to G based on structure and sequence similarities.

They reduce the effectiveness of drugs and contribute to drug resistance in cancer patients. The presence of these drug resistance proteins hinders the action of administered drugs, leading to their limited presence in the cell [50]. P-glycoprotein is an example of a drug efflux pump that is dependent on ATP for its efflux activity. It pumps out chemotherapeutic drugs from inside of the cell to the external environment and ultimately leads to decreased accumulation of drugs inside the cancerous cell [51].

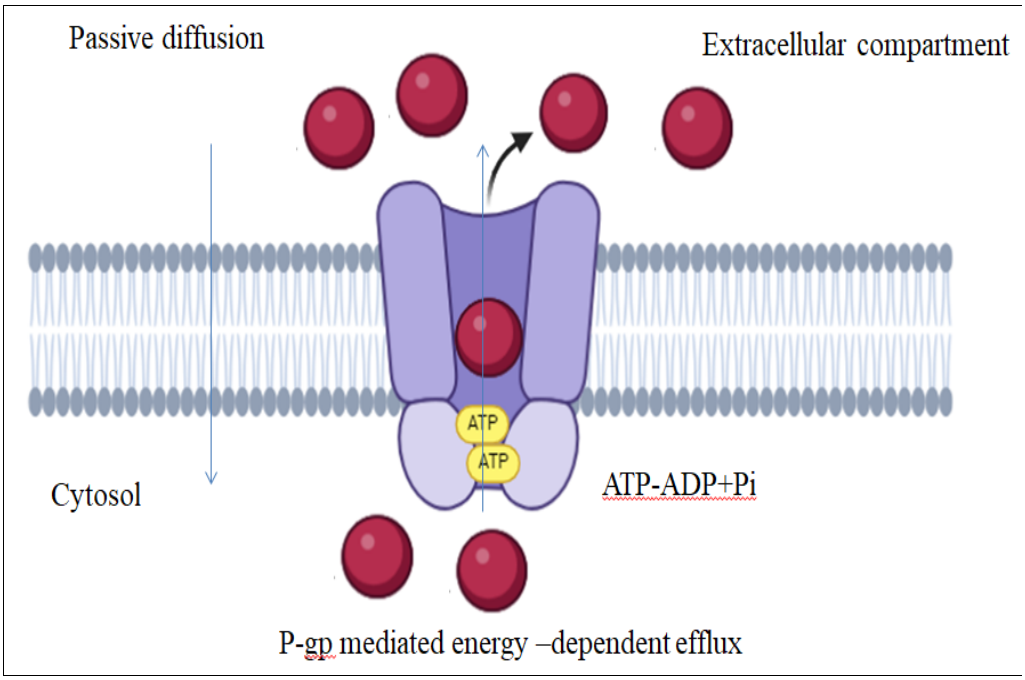

Figure: 3 Efflux of drugs [49]

Gene Mutations:

Gene mutations are typically found in tumor cells and are recognized as a prominent factor in contributing to the ineffectiveness of chemotherapeutic drugs. The frequent loss or rearrangement of chromosomes (aneuploidy) during mitosis is considered responsible for the loss of drug sensitive genes or alterations in biochemical cycles both play important role in the development of resistance to chemotherapeutic drugs [52]. Moreover, the rare chromosomal gains or losses in normal cells generally results in their continued sensitivity to drugs, making the treatment process more complex.Example of one such gene is p53, a tumor suppressor gene which is also referred to as guardian of the genome. Missense mutations in the Tp53 gene are highly prevalent across various types of human cancers. These mutations lead to the formation of mutant p53 proteins that lose their tumor suppressive functions, with some exhibiting trans- dominant repression of the wild type [53]. The retention of these mutant protein forms provides cancer cells with advantages, fundamentally altering the p53 pathway and promoting invasion, metastasis, tumor growth and resistance to chemotherapy. Genetic mutation in Tp53 is thus responsible for continued replication of cancerous cells even in case of DNA damage and makes the cells resistant to genotoxic or chemotherapeutic drugs [54].

High Metabolism of Xenobiotic

Xenobiotic are synthetically composed substances that are foreign to the body. They can be drugs, chemicals, pollutants or anything which is not naturally present in the human body. They are processed inside the human body by the action of enzymes in a systematic metabolic pathway [55]. An example of one such enzyme is Glutathione (GSH). It is an important antioxidant present in living organisms having multiple functions one of which Is maintaining detoxification of xenobiotic. The metabolism of GSH plays dual role both beneficial and pathogenic in malignancies [56]. The process is essential for detoxification and any disruptions in this pathway can directly impact cell survival. In studies, excess level of GSH has been associated with tumor progression and increased metastasis [57].

Another example is a cytochrome isoform CYP1B1 which is found to be elevated in different cancer cells, leading to alterations in the metabolism of chemotherapeutic drugs.

CYP1B1 is found to be elevated in diverse cancer cell types, leading to alterations in the metabolism of chemotherapy drugs like mitoxantrone, flutamide, docetaxel, and paclitaxel [58]. Some chemotherapeutics have been demonstrated to stimulate CYP1B1 in cardiovascular and cancer cells, potentially through the activation of the Aryl hydrocarbon receptor (AhR), ROS production and inflammatory cytokines [59].

Epigenetic Alterations:

Epigenetic alterations are the changes in the heritable gene sequence without affecting the primary DNA sequence. Epigenetic mechanisms encompass alterations in DNA methylation, histone modification and microRNAs (MiRNAs). Genetic mutations and epigenetic alterations both are accounted for the complexity of cancer treatment. Alterations in epigenetic mechanisms can lead to altered gene function and malignant tumor formation. Abnormal epigenetic modification is likely to take place during early stages of neoplastic development and is identified as significant contributors to the progression of tumor [60].

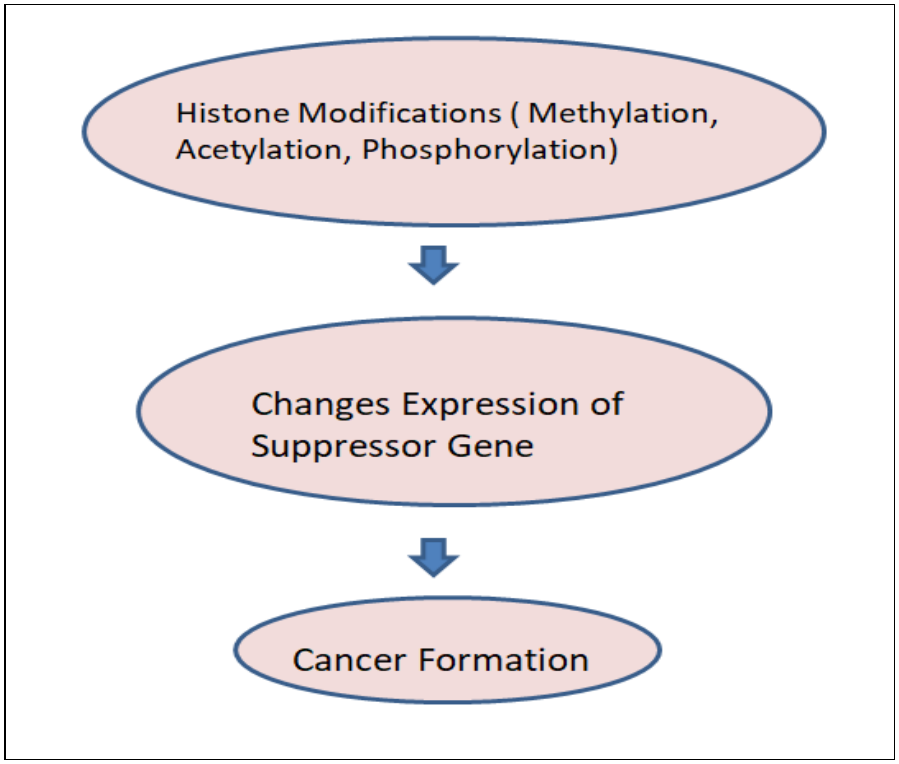

Figure 4 Epigenetic alterations [60-61]

This can be understood by the example of DE methylation of the ABCB1 gene in cancer cell lines, which leads to a reduced accumulation of anticancer drugs within cancer cells, which further results in the development of Multidrug resistance [61].

Gene Amplifications

The phenomenon of gene amplification is observed in about 10% of cancers and plays a crucial role in Multidrug resistance, especially in leukemias. One such drug is Methotrexate; resistance against methotrexate is due to

elevation in quantity of target genes by gene amplification [62].

For example: The upregulation of HER2 (Human epidermal growth factor receptor 2) is observed in approx. 20% of breast cancers. Amplifications in HER2 genes result in transcriptional modifications related to a variety of genes and pathways in breast cancer cells [63]. HER2 altered breast cancers have increased chemotherapeutic resistance. Pertuzumab and trastuzumab are anti- HER2 agents that have been used in HER2 altered breast cancer patients for many years [64]. But the administration of HER2 signaling inhibitors has led to loss of initial drug response and the emergence of MDR [65].

The emergence of Multi drug resistance is indeed a complex process involving increased efflux, High DNA repair capacity, Gene mutations, amplifications, epigenetic alterations etc. The studies of these involved mechanisms of MDR are crucial for the development of new strategies for combating MDR in cancerous cells. The development of new chemotherapeutics can be proven effective to treat MDR and to find a cure for the treatment of malignant tumors [66].

Potential Effective Strategies for Combatting MDR:

MDR in cancer cells makes cancer treatment challenging and leads to progression of cancer. Various efforts for overcoming MDR include new strategies like modified chemotherapy regimens, using different inhibitors of p-gp (p-glycoprotein), focusing on genes related to MDR, development of drugs that are not susceptible to efflux mechanisms of cancer cells. Different types of therapy like Targeted therapy, Immunotherapy, Hormone therapy and Stem cell therapy are also alternative treatment options in case of chemotherapeutic resistance in cancer cells.

Multidrug resistance (MDR) occurs when microorganisms such as bacteria, viruses, parasites, or even cancer cells become resistant to multiple drugs that were once effective for treatment. Strategies to combat MDR can have significant positive effects on global health. One major strategy is antimicrobial stewardship, which promotes the proper use of antibiotics. By ensuring the correct drug, dose, and duration are prescribed, the emergence of resistant strains can be reduced, improving treatment success rates and preserving existing medications.

Research and development of new antibiotics and alternative therapies provide additional treatment options for resistant infections, decreasing mortality rates. Public education and strict government policies regulating antibiotic sales also help minimize misuse. Overall, these combined strategies can slow resistance development, improve patient outcomes, and strengthen global health security.

Modified chemotherapy regimens

This type of treatment is different from traditional chemotherapy protocol as it involves the use of two drugs in varied dosages. The goal is to modify the therapeutic approach based on the specific characteristics of the cancer type. The combination of two different drugs significantly enhances the efficacy of therapeutic treatment by the phenomenon of synergistic effect [67]. This approach reduces the adverse effects associated with single drug administration by allowing for lower doses. This therapy often involves use of different drug classes that act through different pathways, including alkylating agents (such as nitrogen mustard and platinum analogs) [68], antimicrotubular agents (topoisomerase inhibitors and vinca alkaloids) [30], and antimetabolites (including cytidine analogs, folate antagonists, as well as purine and pyrimidine analogs) [69].

Along with lowering toxicities, the combination of two drugs minimizes the chances of developing resistance to a single drug. For example- the combination of cisplatin and etoposide is used in treatment of small cell lung

cancer [70]. Using a distinct combination of drugs in therapy also hinders the emergence of resistant clones by significantly promoting the elimination of highly proliferative metastatic cells.

This treatment is different from Combination therapy in which different treatment strategies like surgery and radiation therapy are combined for effective results.

While creating drug combinations, certain factors are extremely crucial and must not be overlooked like possible metabolic and biological interactions between combined drugs [71], variations in pharmacokinetic profiles, scheduling considerations etc.

P-gp Inhibitors

According to previous research, MDR is associated with overexpression of ABC transporter (p-gp) P- glycoprotein, it is encoded by gene ABCB1 and is also known as MRP1 (multidrug resistance protein 1). Therefore, use of p-gp inhibitors can potentially reduce the drug resistance by contributing to internalization of chemotherapeutics [72].

Technological advancement has led to the development of various types of p-gp inhibitors divided into first, second and third generation.

First Generation p-gp inhibitors:

Examples of first-generation include verapamil, quinidine, cyclosporine A [73].

The limitation of first-generation inhibitors is that they are substrates for certain transporters and enzymes and exhibit pharmacological activity. They are themselves dependent on pgp for their transportation

Second Generation p-gp inhibitors:

Dexverapamil, valspodar, dexniguldipine are examples of second-generation inhibitors [74].

The Second generation of inhibitors are developed from the modification of chiral drugs of first generation by racemic mixtures. Dexverapamil of second generation is an R enantiomer of verapamil of first generation [75].

Third Generation of p-gp inhibitors:

Tariquidar, elacridar and zosuquidar are examples of third generation inhibitors [76].

They are developed to have less toxicity levels and enhanced specificity and effectiveness than first and second generation of inhibitors.

Nanotechnology based approaches:

Organic based supramolecular substances have been developed by researchers like polymers, liposomes and dendrimers [77].

Examples: polymeric substances like PolyRuCHL and polyethylene glycol (PEG) micelles. These substances basically encapsulate chemotherapeutics like cisplatin and doxorubicin with their supramolecular structures [78]. They enhance the delivery of therapeutics by overcoming MDR with the help of distinct endocytosis pathway including receptor and clathirin mediated pathways [79]. Another approach of nanotechnology includes application of inorganic based Nano assemblies.

Example includes use of Hydrophilic terpolymer-MnO2 (TMD), hydrophobic myristic acid- MnO2 (LMD) [80].

Conclusion

In summary cancer and various treatments used to destroy cancerous cells were illustrated. Cancer is the second leading cause of morbidity and mortality worldwide. Millions of deaths are caused due to rapid increasing rate of cancer. Cancer is a complex group of diseases characterized by uncontrolled cell growth and to the others parts of body when abnormal cells grow uncontrollably, go beyond their boundaries to invade the adjoining parts of the body and spread to other organs. Various treatments are used to treat different types of cancer such as leukemia, lymphoma, sarcoma, carcinoma, multiple myeloma, and melanoma. These treatments help to destroy cancer cell by using different drugs as in chemotherapy, by using

radiations that destroy cancerous cells, by boosting immune system response towards cancerous cells, by stem cell transplantation. Along with the cancerous cells the normal cell gets damaged due to the treatment. Various side effects are observed in the patient undergoes the cancer treatment such as pain, anemia, hair loss, nausea vomiting, edema, fatigue, appetite loss etc. Multidrug resistance in cancer cells refers to the ability of cancer to resist the effects of various anticancer drugs that are used against cancer cells. This phenomenon can limit the effectiveness of chemotherapy. MDR often involves the Mechanism such as increased drug efflux, altered drug metabolism, and changes in drug targets. Researchers aim to overcome MDR, developing combination therapies and targeted drug delivery to enhance treatments outcomes. Different types of therapy like Targeted therapy, Immunotherapy, Hormone therapy and Stem cell therapy are also alternative treatment options in case of chemotherapeutic resistance in cancer cells. The phenomenon of MDR resistance in cancer cells is regarded as the main reason for the ineffective treatment of cancer by chemotherapy drugs. Various mechanisms by which cells acquire MDR include gene amplification, efflux of drugs, epigenetic alterations etc. Certain effective strategies to combat drug resistance are present, and can prove to be beneficial in cancer treatment.

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