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DRUG RESISTANCE IN CANCER CHEMOTHERAPY : AN UPDATED REVIEW

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ABSTRACT:

Cancer is a second leading cause of death in the world and chemotherapy is a backbone of treatment for many cancers at various stages. Cancer chemotherapy, a cornerstone of oncology, is frequently hindered by the development of drug resistance. Resistance to chemotherapy is due to variety of factors including individual differences in patient and genetic variances in tumors. The most common cause of drug resistance is a change in expression of one or more energy dependent transporters, insensitivity to drug-induced apoptosis and the production of drug-detoxifying effects. Understanding the complex interplay of intrinsic and extrinsic resistance mechanisms is critical for developing effective treatment strategies to avoid treatment failure. The discovery of specific biomarkers linked to drug resistance can help to inform targeted treatment approaches, allowing chemotherapy regimens to be tailored to individual patients. Furthermore, research into novel drug delivery systems and combination therapies holds promise for overcoming drug resistance challenges.

This review project outlines Status of cancer in the world, types of cancer, various treatments available and drugs available in the market. It also focuses on various aspects of drug resistance in cancer chemotherapy including causes, mechanism of drug resistance and strategies to overcome such drug resistance. This review also includes current knowledge on drug resistance in cancer chemotherapy, providing an in-depth review of the interaction of intrinsic and extrinsic factors. This work aims to inspire innovative therapeutic approaches and facilitate the development of more effective, particular cancer treatment strategies by elucidating the intricate molecular and environmental determinants of resistance.

KEYWORDS:

CANCER, CHEMOTHERAPY, DRUG RESISTANCE, INTRINSIC RESISTANCE, EXTRINSIC RESISTANCE, MDR.

INTRODUCTION

Cancer is a condition when some body cells grow out of control and spread to other body regions. This is result of excessive, uncontrolled, independent, proliferation of tissues as compare to normal tissues of the body. Neoplasia is a Latin word means the new growth of tissues. Neoplasm can be recognised by development of masses of tissues that may be benign or malignant growth [1]. These cancerous tumours grow more aggressive over time and turn fatal when they damage the tissues and organs necessary for the organism's overall survival [2]. Cancer causes the uncontrolled growth of abnormal cells and dynamic alteration of DNA (which cause harmful for ordinary cells). The normal biological functions of healthy cells are disrupted by this disease, which spreads to distant tissues after attacking nearby tissue [3]. After cardiovascular disease, cancer is the second most common cause of mortality in many nations. In many parts of the world, cancer is now or soon will overtake cardiovascular disorders as the leading cause of death [4]. Therefore, it is a fatal disease with a extremely high fatality rate that

affects millions of people's daily lives. This dangerous disease is widespread in developing nations.

Chemotherapy continues to be the primary way of treatment for cancer patients, in addition to surgery and radiotherapy. Over the last few years, significant efforts have been taken to control this disease. Even with advances in targeted therapy, cancer remains the most common cause of death in the world [5]. Cancer drug resistance is a major issue in cancer treatment. Practically any treatment (with the exception of surgery) that is being utilized in the cancer therapy can result into resistance [6]. Cancer patients survival and quality of life have increased due to chemotherapy, but most of them ultimately get progressive disease after initially responding to treatment. A significant barrier to increasing the overall response and survival of cancer patients is drug resistance [7]. Therefore, the focus of this review is to discuss drug resistance in chemotherapy of cancer.

Statistics

One of the worst diseases in the world, cancer claims a large number of deaths each year. More than 10 million new cases of cancer are reported for every year, furthermore, cancer- related deaths are projected to increase in the close future with an assessment by the WHO of approximately 13 million cancer related deaths by

the year 2030 [8]. The global cancer statistics is given in **(Figure 1)**

To e to evaluate changes in mortality rates, one must think about both changes in incidence rates (the number of people with recent cancer diagnosis) and treatment effects. An increase in the incidence of some cancer forms has been attributed to early identification [9]. Although the racial difference in cancer deaths is reducing, social inequalities are expanding with people of the poorest regions facing a greater burden among the most curable cancers [10].This review focuses on a variety of aspects of drug resistance in cancer chemotherapy, including causes, mechanisms, and strategies for overcoming such resistance.

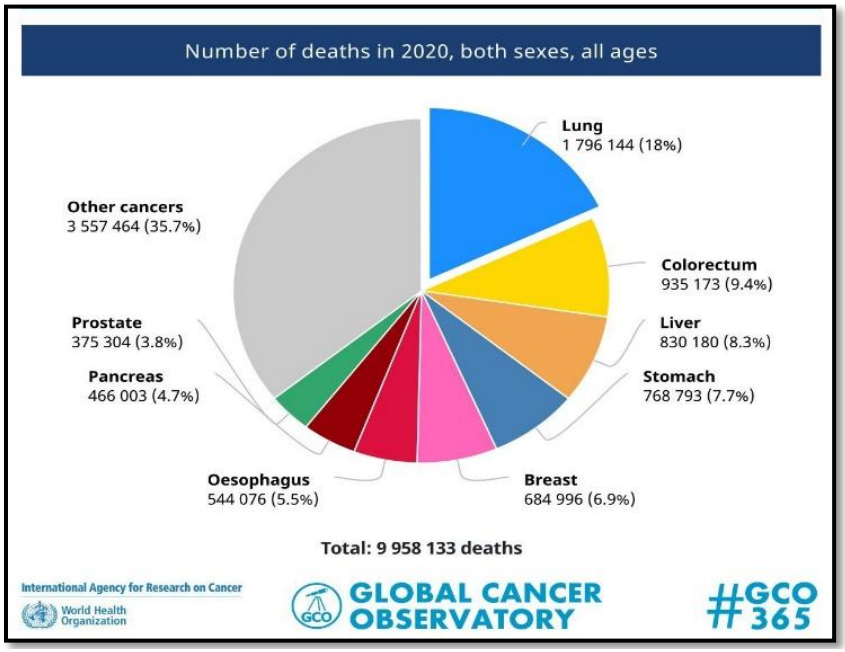

Figure 1: Global Cancer Stastistics 2020

Common Cancers: There are more than 100 cancers which affect people however commonest among all are: Bladder, breast, endometrial, thyroid, colorectal cancer, leukemia, lung (include bronchus), melanoma, kidney (renal pelvis and renal cell) cancer, non-Hodgkin lymphoma, prostate, pancreatic cancer [11] **.**

Treatement of Cancer

Different cancer treatment strategies depend on the size, depth, and stage of the tumour [12]. Depending on the type of malignant growth and the stage of the cancer, a team of oncologists generally develops the cancer treatment (13). Surgery, radiation, and chemotherapy are a few examples of treatment modalities that can be applied singly or in combination, sequentially or concurrently.

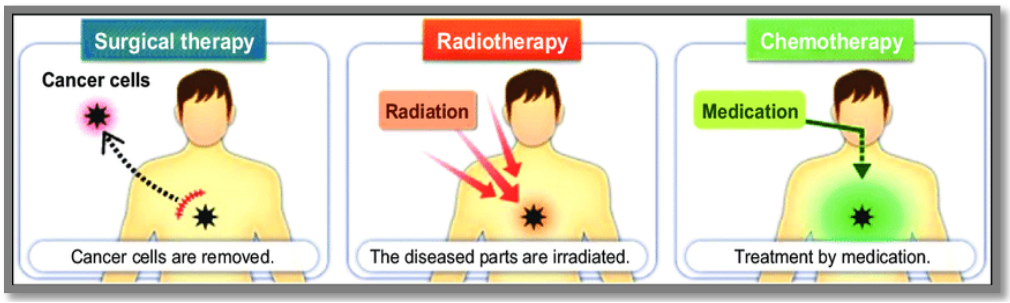

Figure 2: Illustration Of Different Cancer Treatment

- Surgery is usually the first line of treatment and it can be corrective for "early" cancers.
- Radiotherapy is most frequently used and combined with surgeries. Healthy cells, particularly that either divide and develop quickly, as well as organs and tissues, might be harmed by radiation therapy.
- Utilizing medications includes chemotherapy (CTX), which entails the use of different medications with cytotoxic effects that primarily, but not exclusively, target the rapidly dividing cells [13], [14].

The main thing preventing chemotherapy from being successful in treating cancer is the issue of drug resistance. Thus, drug-induced resistance may have a significant effect on the outcome of chemotherapy, implying that factors other than cytotoxicity should be considered when designing treatments [15]**.**

Every cancer treatment aims to completely remove cancer

cells or, at least, permanently prevent their growth. Cytotoxic anti-cancer drugs often disrupt basic cellular processes by generating DNA damage or targeting cell division. They are often administered at the "maximum tolerated dose," making further dosage changes impossible. As a result, any low-level resistance leads in therapy failure [16]. Drug resistance is a complex process that results from changes in drug targets, the development of alternative growth activation pathways, changes in cellular pharmacology, including enhanced efflux of drugs , regulatory changes that alter differentiation pathways or pathways for responding to environmental adversity, and/or changes in the cancer's local physiology, such as blood supply, tissue hydrodynamics, and neighbouring cell behaviour [17]. The efficacy of any pharmacological treatment facility will be determined by how many resistant lines there are in the tumour population and how many treatments are available that can be used in combination. The evidence for drug resistance in human tumours on this basis is largely undefined, but it could explain the apparent success of many drug combinations in situations where single active agents, used alone, apparently to select out a resistant cell line and produce dramatic, but only temporary responses [18].

Table 1: Marketed Formulations for Treatment Of Cancer

Brand name	Company	Drug	Formulation	Route of administration	Application
Abraxane	Abrasix Bioscience	Paclitaxel	Albumin-bound nanoparticle	IV	Metastatic breast cancer
Caelyx	Schering plough	Doxorubicin	Pegylated liposome	IM	Metastatic breast and Ovarian cancer ; Kaposi sarcoma
SPI-77	Sequus pharmaceuticals	Cisplatin	Liposome	IV	Pancreatic, Head and Neck cancer
Stimuvax	Canadian biotech company Biomira Inc.	Tecemotide	Liposomes	SC	Non-small-cell lung cancer
Thermotax	Celsion GmbH	Doxorubicin	Liposome	IV	Hepatocellular carcinoma

CHEMOTHERAPY

Although chemotherapy has a long history dating back to the early 20th century, it was not until the 1930s that it began to be employed in the treatment of cancer. Paul Ehrlich, a German researcher with a focus on alkylating agents, came up with the word "chemotherapy" to refer the use of chemicals to treat illness [19]. Goodman and coworkers coined the term "chemotherapy" at the end of World War II to treat leukaemia and lymphosarcoma chemotherapy has remained a most used method for treating in cancer management but since, a large number of cancer targets and treatment approaches have recently emerged, but resistance and severe side effects remain a major clinical problem [20].

Chemotherapy is the administration of cytotoxic chemicals, for example chemicals with cell killing properties, which in some cases, destroy the growth or, at least, decrease the tumour burden and reduce the cancer related symptoms and maybe prolong life of patients[21]. Although the more sophisticated design of cancer chemotherapy, there is no cancer treatment that is 100% successful against metastatic cancer[22]. Typically, cancer cells multiply more quickly than healthy cells.

Recent research has revealed that some of the medications used in cancer treatment that were found by unbiased screening act by suppressing mitosis and hence cause cell death [23]. Chemotherapeutic agents have a narrow margin of safety and are usually given in combination at a maximum tolerated dose to achieve maximum cancer cell killing. They eliminate tumour cells directly through cytotoxicity or by triggering the immune system of the host, stopping the growth of the tumour cells, and inducing apoptosis [24]. When choosing a chemotherapy regimen for an individual patient, tumour histology and data from clinical studies with a large number of patients have been used to identify which therapeutic option is best for the patients [21].

Chemotherapeutic methods use a variety of chemicals and hormones to interfere with a cell's essential functions. Targeted medicines for some cancer types have been created as a result of this greater comprehension of the molecular changes inherent in cancer cells [25]. Cancer chemotherapy can cure some patients with advanced disease, such as Hodgkin's and non-lymphoma, Hodgkin's acute lymphoblastic and acute myeloma leukaemia, germ cell cancer, small cell lung cancer, ovarian cancer, and choriocarcinoma. Curable malignancies in paediatric patients include acute leukemias, Burkitt's lymphoma, Wilm's tumour. Today, chemotherapy is utilised to treat a variety of solid malignancies. Although these malignancies are not always curable with treatment, progression-free survival has considerably improved [26].

Chemopreventive drugs have been utilized in two ways: to prevent additional DNA damage that would increase carcinogenesis, or to suppress the development of the invasive or metastatic phenotype in the face of known mutation [27]. Chemotherapeutics are classified into two types based on their origin. They can be plant-derived (extracted from plants) or synthetic in nature]. They are classified as antimetabolites, mitotic spindle inhibitors, topoisomerase inhibitors, alkylating agents, and others based on their method [28].

For the majority of malignancies, chemotherapy is the most widely used and effective kind of treatment. Initially, it was believed that chemotherapy drugs would only kill cancer cells, but it is now widely acknowledged that they also damage healthy cells. As a result, there may be side effects depending on the dosage, such as headaches, exhaustion, brittleness, hair loss, diarrhoea, nausea, stomach pains, mouth ulcers, dry mouth, and memory loss. In severe cases, there may even be death [29]. As a result, various types of chemotherapies commonly produce side effects. Over 100 different medications are being used in chemotherapy, either alone or in combination with other types of treatment [30]. The small biochemical differences between host and neoplastic cell tissues contribute to the relatively ineffectiveness of cancer chemotherapy [31]. Cancer chemotherapy failure mechanisms include pharmacological, physiological, and/or cellular mechanisms. First, inadequate medication dosage or ineffective chemotherapeutic dosing regimens may be pharmacological causes of chemotherapy failure. Second, the physiological mechanisms of chemotherapy failure include a lack of optimal distribution of chemotherapeutic agents to what are known as "sanctuary sites" due to the presence of the blood-brain (central nervous system) and blood-testicular (testes) barriers. Poor chemotherapeutic agent distribution to cancer tissue as a result of inadequate angiogenesis vasculature is another physiological cause of chemotherapy failure. Third, Drug efflux transporters, cellular mechanisms that promote chemotherapy resistance, and ultimately failure, Apoptosis, reduced drug uptake, altered drug targets, drug sequestration, increased DNA repair, detoxification, reduced drug activation [32].

Chemotherapy is the backbone of treatment for many cancers at various stages of the disease. Ideally, chemotherapy should only affect highly metabolic, malignant cells and have cytotoxic effects that cause tumours to shrink or increase overall survival. The development or presence of drug resistance, however, is one of the main problems limiting the efficacy of chemotherapy. As a result, chemotherapeutic resistance leads to therapeutic failure and, in most cases, finally death [33], [34]. Since cytotoxic medications have been utilised to treat cancer, there has been a problem with chemotherapy resistance. In clinical trials, it was observed that only some cancers responded to anticancer drugs (intrinsic resistance), whereas others responded, sometimes dramatically, only to become resistant with continued therapy (acquired resistance). Resistance may be limited to the drugs to which patients were exposed (single-agent resistance) or may reflect a simultaneously failure to respond to many drugs with different mechanisms of action multidrug resistance (MDR)[17].

Drug Resistance in Chemotherapy

It is well understood that tumours have an innate ability to resist cancer therapy. In more than 90% of patients receiving standard cytotoxic chemotherapy, exposure to cancer medicines, whether intrinsic or extrinsic DR, is thought to result in treatment failure [35]. A major barrier to the treatment of disease and patients' overall survival is drug resistance, which is decline in a medicine's ability to produce therapeutic effects [36]. Medicine resistance can develop at many periods between the patient's administration of the drug and the desired tumor-cell killing results. These include a) drug metabolic alterations, b) drug penetration into the tumour microenvironment, c) intracellular uptake, d) interactions with the target and e) subsequent signalling events. The combining information regarding all of these variables poses a major issue [37] .

Drug resistance is a term used to describe the phenomena that occurs when diseases become tolerant to medicinal therapies. Chemotherapy resistance is caused by a number of things, such as patient characteristics (such age and gender) and genetic variations in tumours. Changes in the expression of one or more energy-dependent transporters, sensitivity to drug-induced apoptosis, and the generation of drug-detoxifying effects are the three main causes of drug resistance [38]. Though chemotherapy can initially treat a wide range of cancer types, resistance may eventually arise for the reasons and others, such as DNA mutations and metabolic changes that enhance medication inhibition and degradation [39]. The mechanisms that evolved in mammals to defend cells against cytotoxic compounds in the environment will continue to act as barriers to effective cancer treatment, besides the development of newly targeted anticancer therapies. Additional understanding of these cancer treatment resistance processes could help in developing strategies and new drugs that are less sensitive to existing resistance mechanisms [22].

The high failure rate in cancer chemotherapy is due to intrinsic and acquired resistance pathways. Resistance mechanisms or pathways can be classified as pharmacokinetic (i.e. alter intratumor drug exposure) or pharmacodynamic (i.e. failure to elicit cytotoxicity). The resistant phenotype is frequently characterised by changes in multiple pathways. As a result, the pathways may act synergistically or generate a wide range of resistance to anticancer drugs[40]. Two types of variables are mostly responsible for drug resistance. The first set of physiological and pharmacological variables consists of drug excretion and metabolism, insufficient drug availability to the tumour, insufficient infusion rate, and insufficient route of delivery. These are fundamental challenges that are important to drug development as well as clinical practices Factors related to a cell or tissue are included in the second group [41]. The multigene family of

essential, inducible haem-containing oxidative enzymes known as cytochrome P450 enzymes is typically overexpressed in a variety of solid tumours where it can result in treatment resistance. They are crucial to the metabolism of a wide variety of xenobiotics [25]. Drug resistance is a common clinical problem for cancer patients. Various drug resistance mechanisms have been identified. Drug resistance can also be driven on by target mutation or changed expression, as well as defects in the apoptosis, senescence, and repair pathways. As examples, drugs can be prevented from entering the cells, pumped out of cells, enzymatically inactivated, and prevented from entering the cells completely. Multidrug resistance is a special problem in the therapy of cancer [42]. The majority of the most common types of cancer (such as lung, colon, and breast) are characterised by the presence or development of anticancer treatment resistance.

Chemotherapeutic drug resistance may already present at the time of diagnosis or may develop during chemotherapy. Intrinsic and acquired drug resistance are the terms used to refer to such two types of resistance. These two types of medication resistance may or may not be caused by the same causative factors [43]. The theoretical requirements for detecting resistance are based on two fundamentally distinct methods:

- First, the identification of the mechanisms causing resistance to specific drugs or drug combinations, and
- Second, the diagnosis of loss of cancer cell viability upon interaction with test drugs [44].

Chemotherapeutic resistance, whether intrinsic or acquired, greatly lowers the effectiveness of chemotherapy and gives cancer patients a poor prognosis. This resistance is retained to some extent by decreased drug accumulation and increased drug export, changes in drug targets, increased repair of drug-induced DNA damage, evasion of apoptosis, and abnormal autophagy. The emergence of chemoresistance may also be influenced by additional mechanisms and variables, such as cancer stem cells, the tumour microenvironment, epigenetics, and stroma [24].

Types of Drug Resistance

Intrinsic and Acquired drug resistance:

Drug resistance is unavoidable and will eventually lead to treatment discontinuation. Therefore, the issue is not to cure the cancer, but to increase the patient's life span instead. The majority of chemotherapy really fails due to acquired or intrinsic drug resistance, which is not surprising considering the various ways in which the cell may react to cytostatic agent attack [45]. Drug resistance can be categorised as intrinsic or acquired depending on when it occurs. Before to drug therapy, there is intrinsic resistance; whereas, after medication, acquired resistance is produced. Drug resistance occurs in around 50% of cancer patients, either through intrinsic or extrinsic mechanisms, and is responsible for the majority of cancer relapses. Drug resistance, whether intrinsic or extrinsic, is a result of multiple genetic and epigenetic changes in malignant cells.

A) Intrinsic Resistance:

This resistance can be brought on by a number of factors, including: 1) pre-existing (innate) genetic changes that are present in the majority of tumours and reduce the ability of cancer cells like triple critical breast cancer cells, to respond to both chemotherapy and specific medications; 2) tumour heterogeneity, whereby medication treatment will favour previously insensitive subgroups, such as cancer stem cells, leading to recurrence in later stages of therapeutic treatment; and 3) action of inherent defence mechanisms against toxins in the environment (including anticancer drugs).

B) Acquired Resistance:

Acquired resistance may be brought on by: 1) activation of a second proto-oncogene that develops into the driver gene; 2) changed drug target expression levels or mutations; or 3) modifications to the tumour microenvironment (TME) after therapy [46], [47]. Acquired drug resistance is influenced by genetic or environmental factors that promote the formation of drug-resistant cancer cell clones or cause mutations in enzymes involved in relevant metabolic pathways [36]

The resistance mechanisms (intrinsic and acquired) described above may coexist during tumour growth and treatment. Acquired drug resistance can involve mechanisms that are completely different from intrinsic drug resistance. It could also be due to a selective increase in innate drug resistance. The extent of intrinsic drug resistance defines the sensitivity of a cancer cell to a given therapy. Prior to developing a pharmacological therapy strategy, genetic and other biochemical studies should be conducted to eliminate any pre-existing drug resistance. Therapeutic techniques must be modified as a result of the development of acquired drug resistance. One important goal of pharmaceutical therapy must be to successfully inhibit or restrict tumour growth while preventing the development of acquired, or at the very least unmanageable problems [48], [49] .

MDR: Multidrug Resistance

Cancer cell resistance occurs to a number of drugs with different chemical structures and cellular targets, not only to a single chemotherapeutic drug that is used. The term for this phenomenon is multiple drug resistance (MDR)[50] .The resistance phenotype is associated with tumour cells developing cross-resistance to a large variety of drugs targeting different cellular structures which known medically as multiple drug resistance (MDR). MDR is particularly problematic in acquired drug resistance, where using high dose medications to prevent resistance are ineffective and toxic when MDR develops, resulting in less effective chemotherapy. Conversely, MDR is known to be multifactorial, with at least two distinct mechanisms of drug resistance in the same tumour cell [51]. Effective chemotherapeutic therapies against cancer continue to suffer major difficulties due to multidrug resistance

(MDR). This phenomenon has been observed in a range of cancer types and involves cellular and non-cellular processes that cancer cells use to combat the cytotoxic effects of different medications. The pharmaceuticals in concern are structurally and functionally unrelated [52]. Multi-drug resistance (MDR) in cancer treatment is the potential of cancer cells to persist against a number of chemotherapeutic medicines. MDR is characterized by the fact that the development of resistance to one drug results in cross resistance to the other drugs, even though the cells have not been exposed to the other drugs. As a result, the tumour is resistant to antineoplastics that it has not yet been exposed to, and additional chemotherapy with MDR-related drugs is likely to be ineffective. MDR mechanism may be produced by increased drug release outside of the cells. So In these cells, drug absorption is reduced [3], [53]. MDR cell lines are not resistant to alkylating agents, antimetabolites, or cisplatin, but they are to so-called naturally occurring anti-cancer medications such anthracyclines, Vinca alkaloids, and epipodophyllotoxins. Three forms of MDR have been identified: classical MDR, non-Pgp MDR, and atypical MDR [54]. Resistance to therapy is currently the most difficult challenge in cancer. Because each tumour has its own unique set of characteristics that influence tumour progression and can finally lead to death, there are as many underlying resistance mechanisms that exist as people with cancer [55] .

The mechanisms that result in resistance to chemotherapy include drug inactivation, multi-drug resistance, apoptosis suppression, changes in drug metabolism, epigenetic and pharmacological targets, improved DNA repair, and gene amplification [3]. MDR of cancer cells during chemotherapy can be due to a number of mechanisms, such as increased drug efflux, genetic factors (gene mutations, amplifications, and epigenetic modifications), growth factors, increased DNA repair ability, and increased xenobiotic metabolism (Figure 3).

Increased drug-induced DNA damage repair, Apoptosis inhibition, signalling pathway disruptions, and Alteration in cell cycle control factors can also occur which lead to multidrug resistance. Multifactorial multidrug resistance refers to the presence of multiple drugs in cancer cells at the same time. Each of these mechanisms causes a decrease in the therapeutic efficacy of drugs administered, makes the treatment of cancers more difficult [28], [56].

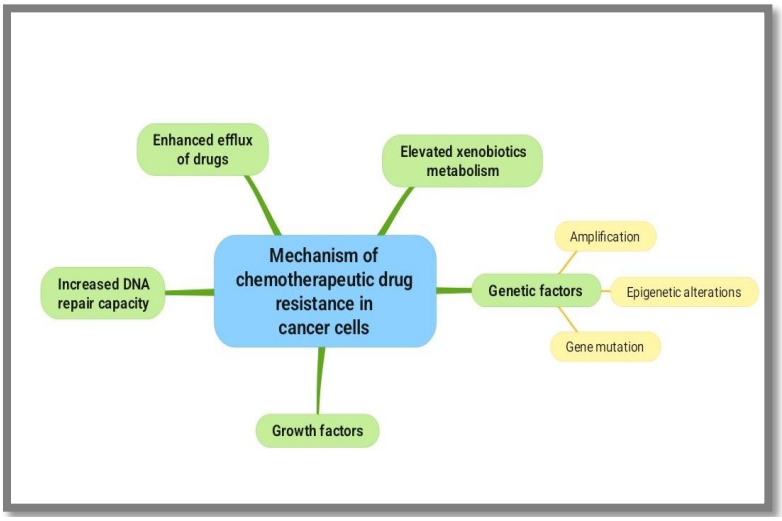

Figure 3: Chemotherapeutic Drug Resistance Mechanisms in Cancer Cells

Mechanisms of chemotherapeutic drug resistance

1. Enhanced efflux of dugs

Physical mechanisms that block or limit drug access to the site of action are one of the most direct ways for tumours to develop resistance to drug treatment. Reducing drug accumulation by increasing efflux is one of the most well-studied mechanisms of cancer treatment resistance. This efflux is facilitated by member of the ATP-binding cassette (ABC) transport proteins, which are important, well-studied modulators at healthy cell plasma membranes. [39]. Drug molecules are expelled from the

cell through a family of ATP-binding cassette (ABC) efflux transporters, which decreases intracellular drug concentration. It is considered to be the primary mechanism for MDR development [57]. In response to tumours from tissues with low expression, those from tissues with naturally high levels of ABC transporters' expression may only show an increase after chemotherapy, acquiring resistance through upregulation of gene expression. These tumours include colon, kidney, pancreas, and liver carcinomas. Tumors from tissues with naturally high levels of ABC transporters' expression may be intrinsically drug resistant. However, in both situations, whether influx/eflux membrane transporters are involved in drug resistance of cancer, depends on how the initial cancer clone evolved in both cases. [5].

2. Elevated xenobiotics metabolism

High-density apolipoprotein is frequently modified by xenobiotics. Due to this, the drug's effective plasma concentration is decreased, while hepatic drug clearance is improved. Overexpression of drug-metabolizing enzymes

or carrier molecules is another physiological reaction to drug presence. For example, increased glutathione or ubiquitin synthesis helps in the inactivation of the drug by producing conjugates that are eliminated. Dihydrodiol dehydrogenase expression is increased in ovarian cancer cells which are resistant to such chemotherapy drug cisplatin [13].

3. Increased dna repair capacity

DNA repair is one of the most well-known drug resistance mechanism in the cancer field. Many anticancer drug works by damaging DNA. Thus, changes in DNA repair enzymes can affect drug resistance. Chemotherapeutic drugs damage the DNA of cancer cells directly or indirectly, but there are various mechanisms available to repair the damage [3], [30]. Many cancer medications, including epirubicin, doxorubicin, 5-fluorouracil, and cisplatin, which have a role as first-line treatments for specific cancers, act mostly by causing DNA damage. DNA damage activates the DNA Damage Response (DDR), which is an important mechanism. Repairing the generated DNA to provide cancer cells a chance for survival lesions, resulting in the development of resistance. But if DDR is absent, Proficiency obviously plays a role in cancer drug resistance. Many cancer drugs work primarily by creating side effects [5]. In general, lethal DNA lesions are excised by DNA repair in cancer cells, therefore it is obvious that Intrinsic drug resistance will be facilitated by effective DNA repair in cancers. failure of one DNA repair pathway may be countered by another compensatory mechanism at work. DNA damage response mechanism, which may help with the resistance to chemotherapy that damages DNA. For example, endoglin inhibition increases cisplatin levels, double-stranded DNA damage, apoptosis, and cell survival [58]. By improving the capacity to remove cisplatin-DNA complexation and repair damages caused by cisplatin through the action of DNA repair proteins, cells can become more resistant drugs like cisplatin. In the early stages of cisplatin resistance, levels of a nuclear protein known as XPE-BF (Xeroderma pigmentosum group E binding factor) were found to increase [8].

4. Genetic factors

Genetic factors such as gene mutation, amplification, and epigenetic alterations can cause drug resistance.

A) Gene Mutation

Drug resistance can develop through adaptation or mutation. Adaptation is induced by the drug and is dependent on the drug's continued presence; resistance is rapidly lost when resistant cells are grown in the absence of a drug . Drug resistance mutations can occur in both the presence and absence of the drug. [59]. Cancer cells frequently face gene mutations; in fact, it is this process that gives the cancer cell its distinctive properties. Cytotoxic medications try to disable a component whose continuous function is required for cell survival; cells that survive the treatment may achieve this by carrying a gene for that target that has mutated in such a way that it creates a protein that retains its activity but, for stereochemical reasons, no longer binds to the drug and is thus not inhibited by it. As a outcome, the drug is no longer effective in the cell [13]. Mutations that alter the activity or reduce the appearance of specific receptors and transporters can lead to resistance. For instance, the extracellular receptor was smoothened by mutations or reduced expression, Nucleoside transporters or one or both folate transporters lead to poor uptake of cyclopamine, toxic folate analogues such methotrexate, and nucleoside drugs like cytarabine [60] .

B) Amplification

Cells can develop drug resistance by amplifying and overexpressing drug-resistance genes. A mechanism known as gene amplification has been associated to drug resistance to methotrexate, N-phosphonoacetyal-L-aspartate, and several other drugs [61]. Amplification of a gene is defined as a rise in the count of copies of that gene present in the cell after cell division, whereas deamplification is defined as a decrease in the count of copies. cancer cells are genetically unstable due to mutational changes and Cells can acquire more copies of genes due to gene amplification during cell division. As a outcome, the cells become more resistant to certain drugs, such as by addition of genes that help in drug elimination or metabolization The more copies of such gene will be present, the more resistant the cells become to even higher levels of the drug's concentrations As a result, gene amplification is well-documented as one of the reasons for cancer cells developing drug resistance [45]. Gene amplification is a mechanism of chemoresistance in 10% of cancers, particularly leukemias. The number of target genes for the gene has increased. leukaemia and some tumoral cells amplification cause of Methotrexate drug resistance. Drug resistance is brought about by cancer cells producing extra copies of the gene for dihydrofolate reductase, an enzyme that may be a target for methotrexate. The oncogenes copy counts per cell are multiplied by several hundred due to gene amplification. Finally, this pathway increases the production of associated oncogenes [3].

C) Epigenetic Alterations

The altering of epigenetic changes is one of the significant mechanisms of drug resistance in cancer treatment. Histone modifications and DNA methylation are the two main types of epigenetic altering [3]. According to one study, chromatin structural alterations and hypermethylation of the MDR1 promoter are linked to transcriptional suppression. DNA methylation has additionally been linked to acquired multidrug resistance, according to other theories. Demethylation of the MDR1 promoter in cancer cell lines was investigated in research extending this theory Cancers discovered to be closely related to the development of a multidrug resistant phenotype. Overall, MDR1 transcription is regulated by methylation at this promoter, which also boosts drug resistance and lowers drug accumulation, which makes it a great target for epigenetic therapy. In particular,

anti-methylation drugs could be helpful in making drug-resistant cancer cells more susceptible to other types of drugs. Overall, epigenetic changes are now more widely recognized as a factor in drug resistance in a variety of cancers. So, in addition to conventional and targeted chemotherapy, epigenetic therapy could be used as a priming therapy to make drug-resistant cancer cells susceptible [39].

5. Growth factors

Several components, such as growth factors, cytokines, hormones, etc. are common in the cancer cells. When macrophages, fibroblasts, or other cells which promote tumour growth are transformed into tumor-promoting cells, they release growth factors and cytokines as well as neutrophils, which are anti-tumorigenic cells. Growth-promoting elements through a number of signalling pathways, angiogenesis helps tumour survival. The disruption of homeostasis by numerous growth factors is known to cause disease development and drug resistance to many drugs [62]. In addition to intracellular factors, the presence of external fibroblast growth factors at higher levels in the metastatic and solid tumour cells can further increase cancer chemoresistance. According to data, treatments with various modes of action, such as 5-FU, DOX, and paclitaxel are unsuccessful against tumours containing high levels of these extracellular factors. Suramin, a well-known inhibitor of these factors was used by Song et al. to demonstrate the significance of fibroblast growth factors in the development of cancer chemoresistance. Suramin successfully reversed the 10-fold increase in resistance caused by the combination of intracellular and external variables [28]

Approaches to overcoming drug resistance

The main limitation of current cytotoxic cancer treatment regimens is drug resistance (the failure of tumours to react to chemotherapy or the emergence of relapse with disease that is resistant to additional treatment following a preliminary response). There are two basic techniques for changing this situation: developing new treatments and applying existing therapies more effectively. The research of drug resistance molecular processes should contribute in both strategies, allowing for the discovery of new drugs (or combinations of therapies) to overcome drug resistance along with the more sensible selection of existing therapies for defined groups of patients [37] . As the drug resistance mechanisms become more clearer, some approaches to resolving this problem include beginning to emerge. Combination drug treatment is the simplest and most commonly used solution. The general principle for selecting which drugs to combine is to use medications that are effective against the tumour when used alone; to combine those that have various modes and sites of action to produce complementary or synergistic effects rather than just additive effects; to combine those that have minimally overlapping toxicities, allowing administration of the highest possible doses of each active agent to allow for the best possible planning of each drug; and to use those that have narrow therapeutic window [13] .One therapeutic approach to overcoming drug resistance is "treatment holidays" which involves temporarily stopping a patient's chemotherapy as a treatment prevent the selection of drug-resistant tumour cells that maybe result in cancer recurrence and relapse [36] . To prevent the MDR mechanism, various nano-drug delivery systems such as solid lipid/mesoporous silica/ polymeric /metal nanoparticles, dendrimers, liposomes, micelles, and nanostructured lipid carriers have been developed [63]. Immunotherapy has long been proposed as a solution to many of the problems associated with anti-cancer drug resistance [64].

Cancer cells with a greater amount of drug-accumulating lysosomes are sensitive to lysosome - sequestered drugs, suggesting a drug-induced lysosome-mediated chemoresistance model. . In addition to passive drug absorption of water - insoluble weak base chemotherapeutic drugs, several mechanisms of lysosomal drug resistance have been discovered. It included active lysosomal drug absorption mediated by ATP-driven ABC superfamily transporters and a role of autophagic copper transporters in platinum-based chemotherapeutic resistance. Furthermore, lysosomal exocytosis has been suggested as a way to help in the chemotherapeutics clearance that have greatly accumulated in lysosomes, providing an extra line of resistance to chemotherapeutic organelle entrapment away from their intended targets. In addition to these lysosome-mediated drug resistance mechanisms, several approaches to drug resistance has recently been discovered e.g, alkalinization to inhibit lysosomal sequestration of chemotherapeutics and targeting of the lysosomal compartment in order to cause lysosomal membrane lysis might be promising strategy for overcome drug resistance [65] .

Autophagy has both tumour suppressive and oncogenic properties in cancer. It is generally recognized that inhibiting autophagy in cancer cells can overcome drug resistance [66]. Drug resistance, particularly MDR, has been identified as the most severe problem in the oncological society including among patients. Although a significant amount of proteins, genes and biochemical pathways have been identified and described, complex molecular networks impede strategies for combating MDR throughout a particular target. MDR results in apoptotic resistance. As a result, natural products may be used to prevent or treat drug resistance in cancer chemotherapy by using several ways. Controlling MDR and increasing intracellular concentrations of chemotherapy agents is a well-studied strategy. This involves inducing nonapoptotic cell death processes such as necroptosis and autophagy and oncosis. [67] .

Recently, a number of effective methods for controlling MDR have developed using natural resources like plants, fungus, and even marine organisms. These modulators are well tolerated by humans and have low toxicity. The ABCB1 and ABCG2 transporters are substrates for a significant portion of these natural modulators. During These modulators compete with cytotoxic substances

when administered together. for interacting with these transporters' active side to decrease drug efflux. More importantly, the majority of phytochemicals have a multiple anticancer effect [68]. Because of the remarkable carcinogenic activity of its constituents (including YAP and TAZ) and their druggable properties, the Hippo signalling pathway is one of the mechanisms that have been identified to produce anti-cancer drug resistance. the Hippo signalling system controls tumour cell generally pro drug resistance and also currently available pharmacological therapies that target the Hippo pathway to kill cancerous cells and possibly treat cancer patients [69].

Researchers have recently created more sophisticated delivery systems by introducing tumour attracting ligands and combining stimuli sensitive characteristics to multifunctional (targeted) nanosystems in an effort to maximize the utility and capabilities of nanoparticles-based delivery systems. To achieve a better therapeutic outcome, these systems can use both passive and active tumour targeting principles, along with a variety of drug/gene release mechanisms. Such precision-guided multifunctional nanosystems have the potential to be extremely useful in the treatment of MDR cancers [70].

Overall, several common anti-MDR approaches at the present may be summarised into a general strategy, namely the synergy therapy of two or may be more drugs by using one of the gene/drug to block ABC transporters and the other chemotherapeutic drug to destroy cancer cells [71] .

Conclusion

Combining chemotherapy with newer cytotoxic and biologic therapies is an effective strategy for combating tumour growth and/or progression. These combinations can make it easier to attack multiple intercellular processes, potentially leading to more effective tumour responses. Drug resistance is a major issue limiting cancer chemotherapy success. Multidrug resistance is a complicated process that involves increased drug efflux, increased xenobiotic metabolism, increased DNA repair capacity, growth and genetic factors, or any combination of the above. Although drug resistance mechanisms are a big problem for cancer patients, understanding the mechanism of resistance may lead to new treatment options for subsequent therapy. **Review highlights the mechanisms of resistance to cancer drug treatment chemotherapy and various approaches to overcome this problem.**

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