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AN OVERVIEW OF FACTORS INCREASING THE RESISTANCE TO ANTI-CANCER DRUG

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Abstract:
One of the major causes of chemotherapy failure in cancer is drug resistance to conventional therapy. Tumor heterogeneity, some cellular level changes, hereditary variables, and other unique mechanisms have all been identified as underlying causes for drug resistance development in tumors in recent years. We searched the literature from the year 2000 until the end of 2021 for all relevant articles that discussed the elements that increase anti-cancer drug resistance. Drug delivery systems containing a targeting moiety improve site-specificity, receptor-mediated endocytosis, and drug concentration inside cells, reducing drug resistance and improving therapeutic efficacy. These therapeutic techniques function by regulating the various drug resistance pathways.

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INTRODUCTION:

Cancer is responsible for around one in every six deaths worldwide. With 8.7 million fatalities in 2015, it is the world's second greatest cause of death [1]. Tobacco use (22% of cancer fatalities), lack of physical activity, alcohol use, low vegetable and fruit intake, and a high body mass index are all related with an increased risk of cancer. These factors are considered to be responsible for one-third of all cancer deaths. Women are more likely to develop breast, cervical, lung, thyroid, and colorectal cancers, while men are more likely to develop prostate, lung, colorectal, liver, and stomach cancers [2]. Medication resistance and the ineffectiveness of medication treatment account for up to 90% of cancer-related deaths [3,4].

Cancer drug resistance is a well-known condition that occurs when cancer grows resistant to medicinal treatment. Anticancer medication resistance is caused by a variety of causes, including genetic mutations and/or epigenetic alterations, conserved but increased drug efflux, and a variety of other cellular and molecular pathways [5].

Surgery, cytotoxic chemotherapy, targeted therapy, radiation therapy, endocrine therapy, and immunotherapy are the most commonly used cancer treatments today [6,7]. Despite advances in cancer treatment over the last few decades, resistance to traditional chemotherapeutic agents and/or innovative targeted medications remains a major issue in cancer therapy, accounting for the majority of relapses and one of the leading causes of death [3,8]. Many traditional chemotherapeutic anticancer medicines kill cancer cells by directly destroying their DNA, which has the disadvantage of being non-specific and relatively toxic. More and more targeted medications have been created in recent decades to precisely target/block alterations that promote cancer growth and proliferation. Although these medications have great results in the beginning, the vast majority of individuals acquire resistance as treatment progresses. For example, 30%-55% of non-small cell lung cancer (NSCLC) patients relapse and die from the disease [9]. Within one year of surgery and concomitant chemotherapy, 50%-70% of ovarian adenocarcinomas reoccur [10]. Recurrence occurs in around 20% of pediatric acute lymphoblastic leukemia patients [11].

DISCUSSION:

Multi-drug resistance (MDR) in cancer chemotherapy has been defined as the ability of cancer cells to survive against a wide spectrum of anti-cancer medications [12]. Increased drug release outside the cells may result in the development of an MDR mechanism. As a result, medication absorption in these cells is reduced [13].

Increasing the release of drugs outside the cell:

There is an ATP-dependent transporter family that is involved in the transport of nutrients and other substances across the membrane. The ABC transporters are made up of two cytoplasmic ATP-binding cassette (ABC) domains and two transmembrane domains (TMDs) [14]. P-glycoprotein (PGP), multi-drug Resistance-associated Protein 1 (MRP1), and Breast Cancer Resistance Protein (BCRP/ABCG2) are members of the ABC Family [15]. P-Glycoprotein (P-gp) is a multidrug membrane transporter that normally functions as a pump for moving chloride out of cells and can bind to a variety of chemotherapy agents, including Doxorubicin, Vinblastine, and Taxol, after binding ATP is hydrolyzed and the structure of P-gp is altered. As a result, the agent exits the cell and enters the extracellular area. After the second ATP hydrolysis, the transporter recovers to its basic structure and can deliver the medication outside of the cell (Figure 1) [16].

Chemotherapeutics are classified into two types based on their origin. They can be plant-derived (extracted from plants) or synthetic in nature [17]. They are classified as alkylating agents, antimetabolites, topoisomerase inhibitors, mitotic spindle inhibitors, and others based on their mechanism of action (**Figure 1**) [18].

Alkylating agents include the oxazsaphosphorines (cyclophosphamide and ifosfamide); nitrogen mustards (busulfan, chlorambucil, and melphalan); hydrazine (temozolomide); platinum-based agents (cisplatin, carboplatin, and oxaliplatin) [19]; and novel, still under investigation OFF-ON-type alkylating agents such as vinyl-quinazolinone (VQ) [20]. Chemotherapeutics in this family produce inter- or intra-strand cross links or transfer alkyl groups to DNA guanine residues, resulting in mispair formation in DNA bases and preventing strand separation during DNA synthesis [21].

Antimetabolites can be divided into several groups: pyrimidine antagonists (cytarabine, 5-fluorouracil (5-FU), gemcitabine, and capecitabine), purine antagonists (fludarabine), purine analogs (6-mercaptopurine, azathioprine, and cladribine), antifolates (methotrexate, pemetrexed, and

pralatrexate), and ribonucleotide reductase inhibitors (hydroxyurea). Through inhibition of specific enzymes (dihydrofolate reductase, ribonucleotide reductase, and DNA polymerase) or incorporation of false structural analogues of pyrimidine/purine into DNA, these anticancer drugs disrupt essential biosynthetic pathways, disrupt DNA/RNA synthesis, or cause the formation of DNA strand breaks [22].
Topoisomerase I inhibitors (irinotecan and topotecan) and topoisomerase II inhibitors (etoposide, teniposide, and anthracyclines such as idarubicin, daunorubicin, and doxorubicin (DOX)) inhibit topoisomerases and cause DNA strand breaks [23].

Taxanes (docetaxel and paclitaxel) and vinca alkaloids (vincristine (VCR) and vinblastine) change spindle microtubule function/formation by inhibiting nucleus division (mitotic arrest in metaphase), resulting in cell death [23].

Peng et al. [24] recently demonstrated that one of the newly synthesized N-carbonyl acridines inhibited tubulin polymerization, exhibiting high antiproliferative activity against human mammary gland/breast cancer cells MB-468 (IC50 value comparable to colchicine and paclitaxel).
Other chemotherapeutic drugs with non-homogenous modes of action include certain enzymes (l-asparaginase), proteasome inhibitors (bortezomib), tyrosine kinase inhibitors (imatinib and erlotinib), and antibiotics (bleomycin, actinomycin D, and anthracyclines). While l-asparaginase cleaves the amino acid l-asparagine, which is required for normal cell metabolism, bortezomib induces apoptosis by inhibiting apoptotic protein degradation. Imatinib and erlotinib suppress the activity of tyrosine kinases that are engaged in several intracellular pathways linked with receptor-mediated growth signaling, resulting in cellular malfunction and cell death. Bleomycin, an antibiotic, causes free radical production, which causes DNA damage and cell cycle arrest in the G2 phase. Actinomycin D, another anticancer drug, intercalates into DNA and interferes with DNA transcription. Anthracyclines decrease topoisomerase II activity and have anti-proliferative effects in the aforementioned processes [25].

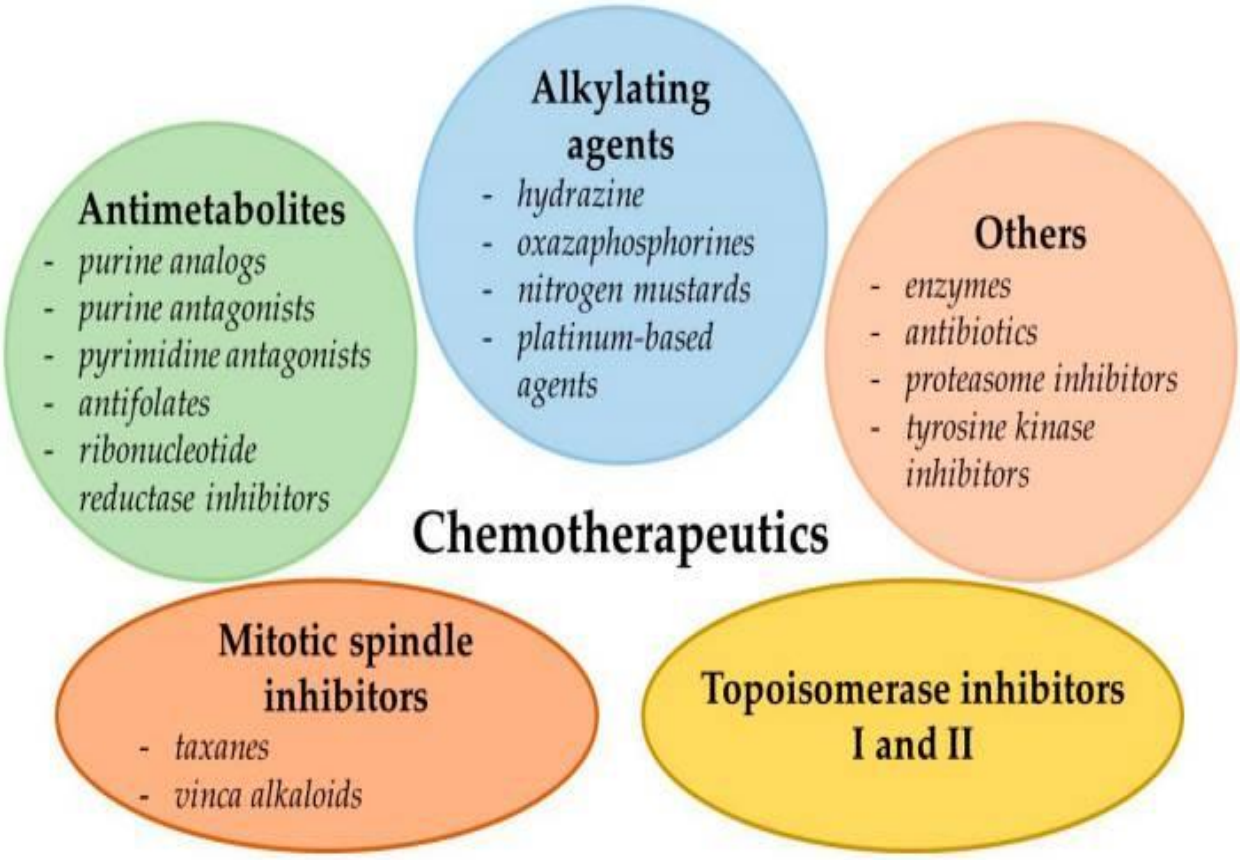

FIGURE 1. Classification of commonly used chemotherapeutics depending on their mechanism of action

Enhanced Efflux of Drugs

P-glycoprotein (P-gp)/ATP-binding cassette subfamily B member 1 (ABCB1) or Breast Cancer Resistance Protein (BCRP) are ATP-binding cassette (ABC) proteins found in the cell membrane that regulate the distribution, absorption, and excretion of a variety of chemical substances. Because these proteins protect cells from cell death caused by high intracellular drug concentrations, they can also interfere with drug administration by reducing bioavailability, intracellular concentration, and BBB transition. P-gp, which is extensively expressed on the endothelial cell surface, contributes to limited chemotherapeutic drug penetration to specific areas, particularly in the treatment of brain tumors, where anticancer medicines are often incapable of passing through the BBB. The size of the tumor is also important for drug penetration. Chemotherapeutic drugs are typically less effective in large tumors because to the low blood supply, compared to tiny tumors with practically unrestricted access to oxygen and nutrition supply. The P-gp defends the brain from potentially harmful substances while also limiting access to therapeutic medicines that are responsible for the higher complexity of the therapy. In most circumstances, the only method to overcome the barrier is to increase the drug concentration, which frequently results in systemic toxicity. This is why increased drug efflux has been identified as one of the primary mechanisms of cancer cell resistance to chemotherapeutics [9,14,15,17].

P-gp and BCRP can eliminate from cancer cells a wide variety of structurally and functionally unrelated anticancer agents, including epipodophyllotoxins, anthracyclines, vinca alkaloids, bisantrene, colchicine, taxanes, imatinib, saquinavir, camptothecins, thiopurines, actinomycin D, methotrexate, and mitoxantrone to the extracellular space, reducing intracellular drug accumulation [14,15,18,19,20]. Significant correlations have been identified between higher P-gp expression in cancer cells and increased resistance to paclitaxel, etoposide, olaparib, DOX, and vinblastine [23,24]. P-gp overexpression has been observed in approximately 50% of all human malignancies. While increased P-gp expression has been observed before chemotherapy treatment in some tumor types such as lung, liver, kidney, rectum, and colon, overexpression of P-gp has been observed after chemotherapy treatment in others, including hematological malignancies such as acute lymphoblastic leukemia and acute myeloid leukemia [15,20]. P-gp and BCRP overexpression has been linked to poor clinical response and MDR in patients with multiple myeloma, acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia, and metastatic breast cancer [18]. Furthermore, it has been reported that P-gp plays a role in cancer cell MDR not only by participating in intracellular chemotherapeutic agent efflux but also by inhibiting tumor necrosis factor-related apoptosis-inducing ligand TRAIL-mediated and caspase-related apoptosis pathways [19,25,26].

Although P-gp inhibitors have demonstrated excellent efficacy in in vitro and in vivo investigations, none have been licensed for clinical use in cancer treatment by the US Food and Drug Administration (FDA) [18,27]. However, Nanayakkara et al. [26] reported some new P-gp inhibitors that could be promising cancer chemotherapeutic medicines. Despite the fact that clinical trials have not yet begun, researchers using a computational approach discovered numerous compounds capable of inhibiting P-gp activity and confirming their anticancer capabilities against MDR cancer cell lines. Furthermore, Nanayakkara et al. [26] examined chemotherapeutic coadministration with the studied compounds against two-dimensional MDR prostate and ovarian cancer cells as well as three-dimensional prostate cancer microtumor spheroids. Cell motility, as well as cell survival and viability, were shown to be significantly reduced. Furthermore, the researchers revealed that none of the tested P-gp inhibitors were hazardous and were not P-gp transport substrates. Furthermore, examined substances improved not only anticancer drug cellular retention but also the number of reporter compounds that are P-gp transport substrates [27].

Genetic Factors

Gene mutations, which are widely detected in tumor cells, are thought to be one of the primary causes of chemotherapy treatment failure. According to Duesberg et al. [28], the best explanation for MDR formation in cancer cells is their aneuploidy. Researchers believe that recurrent chromosome losses or reassortments during mitosis are responsible for the loss of drug-sensitive genes or alterations in biochemical pathways, both of which appear to be important in chemotherapeutic drug resistance. Furthermore, normal cells, which seldom gain or lose a chromosome, frequently remain susceptible to medications, making treatment even more difficult.

Mutations in the TP53 gene, which are frequently found in tumor cells, are one of the most well-known indicators of carcinogenesis. According to Mantovani

et al. [29], forty years of research have established the TP53 gene's crucial role in defending an organism against neoplastic transformation and tumor growth. The TP53 tumor suppressor is in charge of genome stability and cellular homeostasis by coordinating numerous processes and effector pathways, such as cell cycle regulation and initiating apoptosis or G1 arrest in the event of genotoxic stress during replication. Missense mutations in the TP53 gene, which are particularly common in human malignancies, reverse the protective role of the TP53 pathway by beginning chemoresistance, invasion, and metastasis. Anticancer medicines that cause DNA damage normally cause cell death via TP53 activation. In contrast, loss of TP53 activity in cancer cells allows them to continue replicating regardless of the type/level of DNA damage, making them resistant to genotoxic medicines [29].

Amplifications

Many chemotherapeutics, such as methotrexate, work by inhibiting important enzymes, such as dihydrofolate reductase, which controls cell proliferation. Because of the possibility of gene amplification, which occurs in 10% of malignancies, primarily leukemias, cancer cells can overcome this inhibition by increasing transcription of the gene encoding the enzyme. This mechanism is connected with the selective synthesis of a specific chromosomal area, which results in multiple copies of the same gene. These amplified sequences are distinguished by the presence of homogeneously stained areas or double minute chromosomes. Each of those genes is transcribed to increase the level of mRNA, which is then used in the translation process to make additional enzymes. Because the medication concentration is limited, it can no longer inhibit the increased amount of enzyme [30].

Using The Cancer Genome Atlas (TCGA), Zhang et al. [31] evaluated the transcriptomics, genomes, and clinical data of a range of cancer samples, particularly breast cancer (1082 samples). As a result, substantial connections were found between amplification of the glycosylphosphatidylinositol-linked cell surface glycoprotein (CD24) gene and TP53 gene alterations, cancer proliferation, and metastasis. A copy number variation of CD24, according to the researchers, could provide as a simple potential prognostic marker for identifying populations of interest for cancer treatment and risk classification.

Intrinsic and extrinsic factors in drug resistance

Tumor heterogeneity

Intra-tumor heterogeneity can be exhibited at a variety of cancer levels and may be attributed to a variety of variables that predominantly occur at the cellular level. This refers to the natural emergence of variations with diverse genomic, epigenetic, transcriptomic, and proteomic features. Mutations, gene amplifications, deletions, chromosomal rearrangements, transposition of genetic elements, translocations, and microRNA alterations are examples of genotypic changes. In cancer, genomic instability leads to a high amount of intercellular genetic heterogeneity. According to the cancer stem cell hypothesis, epigenetic factors such as miRNA, transcriptome, and proteomic heterogeneity may increase due to fundamental genotypic differences, but they can also reflect cell cycle stage, stochastic variations between cells, or hierarchical cell organization [32]. Intrinsic factors are the changes that cause tumor heterogeneity. pH, hypoxia, and paracrine signaling connections with stromal and other tumor cells are examples of extrinsic factors [32].

Tumor microenvironment

Growing data supports the importance of the tumor microenvironment in drug resistance discussions as the primary cause of cancer relapse and incurability. Normal stromal cells (SC), extracellular matrix (ECM), and soluble substances such as cytokines and growth factors are all present in the tumor microenvironment. Tumor-tumor cell communication, tumor-stromal cell communication, and tumor-ECM interface all contribute to drug-mediated direct cell interaction [31,32]. Furthermore, tumor-derived growth factors (GF) and cytokines give additional signals for tumor cell development and survival. VEGF (vascular endothelial growth factor); bFGF (basal fibroblast growth factor); SDF-1 (stromal cell-derived factor-1); IL-6 (interleukin-6); NO (nitric oxide); IL-3 (interleukin-3), G-CSF (granulocyte colony stimulating factor); M-CSF (macrophage colony stimulating factor).

Cancer stem cells

Cancer stem-cell populations have been seen in a range of hematological and solid malignancies, and they may represent the source of these tumors. Although chemotherapy affects a large number of cells in a tumor, it is understood that chemotherapy agents are removed from cancer stem cells via special mechanisms that may be important for drug resistance. For example, overexpression of the ATP-binding cassette (ABC), drug transporters such as ABCB1, which encodes P-glycoprotein, and ABCG2, which was first identified in mitoxantrone resistant cells, have been shown to keep cancer stem cells alive. Cancer stem cells have several properties that normal

stem cells do not, such as relative silence, resistance to drugs and toxins through the expression of drug efflux transporters, an active DNA-repair capacity and resistance to apoptosis, vascular niche, dormancy, hypoxic stability, and increased activity of repair enzymes [33].

CONCLUSION:

Small compounds, peptides, and nanotherapeutics have evolved to combat cancer medication resistance. Drug delivery systems containing a targeting moiety improve site-specificity, receptor-mediated endocytosis, and drug concentration inside cells, reducing drug resistance and improving therapeutic efficacy. These therapeutic techniques function by regulating the various drug resistance pathways. Tumor cells differ from normal cells in their phenotypic and morphological profiles, which include cellular morphology, gene expression, epigenetic, motility, metabolism, proliferation, transcriptome, and metastatic capacity.

Because cancers are virtually usually multi-clonal and genetically diverse, combination therapy are widely desired. Because the therapy kills sensitive cancer cells while allowing resistant cancer cells to live and grow, single-drug therapeutic techniques are most likely to result in treatment failure due to drug resistance. Combinational therapy with two or more medications, on the other hand, is likely to target many driver genes at the same time, not only suppressing more clones in a tumor but also making new cancer mutations resistant to multi-drug treatment much more difficult to select and grow up. Current drug resistance management options rely on ongoing patient monitoring and therapy with a cocktail of chemotherapeutic/target medicines, each targeting one or more proteins encoded by driver genes responsible for drug resistance pathways in cancer patients.

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