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CHEMO RESISTANCE: A MAJOR HURDLE OF CANCER THERAPEUTICS

PATEL A[1], SHAH S[2], PANCHAL I[3]

1. Assistant Professor, Pharmacology Department, Sardar Patel College of Pharmacy, Bakrol-Anand, Gujarat.
2. Principal, Sardar Patel College of Pharmacy, Bakrol- Anand, Gujarat.
3. Assistant Professor, Pharmaceutical Chemistry Dept. SPCP, Bakrol.

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Abstract: Cancer is today's second leading cause of mortality in world. The therapeutic options available for that are chemotherapy, radiation, hormonal therapy and surgical ablation. The major obstacle in cancer therapeutics is resistance of tumor cells similar to micro organism involved in infection. Resistance may be defined as lack of therapeutic response by drug although the dose and efficacy of drug correct. Resistance may be inherited property of cell or it acquired over period of time once drug therapy started. The important mechanisms responsible for drug resistance are defective transporter, deny apoptosis pathway after insult, mutated enzyme that may be metabolic enzyme, target enzyme or enzyme linked to DNA repair. Some time resistance may overcome by increased dose that subsequently leads to increased toxicities. Many new ways are utilized for avoid or delay of resistance like inhibitors of P-glycoprotein, protein kinase C. Resistance may responsible for longer hospital stay, increase in cost of therapy and therapeutic failure to many chemotherapeutic agent. Ultimately it will be burden on phrmacoeconomic of patients and affecting prognosis of disease.

Keywords: Cancer, Multiple Drug Resistance, P-Glycoprotein, Tyrosine Kinase, Chemoprevention

Corresponding Author: MR. ALKESH PATEL

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INTRODUCTION

Cancer or neoplasm defined as abnormal new growth due to uncontrolled proliferation, lack of differentiation, immortality and unable to kill by apoptosis. The uncontrolled proliferation ultimately transform to tumor. Although variety of treatment options are in hand but cancer mostly remain incurable after crossing certain stages. Plenty of cytotoxic drugs are available that includes alkylating agent, inhibitors of cell division, intercalating agents but main drawback of this drug is that non selective killing of normal body cells. Activation of nuclear factor kappaB (NF-κB) and activator protein 1 (AP-1) transcription factor by Protein kinase C (PKC) and phosphatidylinositol 3-kinase (PI3K) responsible for metastasis and invasive of many cancers [(1)].

Tumor made up of either chemotherapy sensitive and insensitive or resistance cells. When tumor is targeted by anticancer drug, it will kill sensitive cells but leaving behind population of resistance cells. While these resistance cells are proliferates, it give birth to resistance progeny. Multiple drug resistance (MDR) is today's major problem of chemotherapy that may be intrinsic or acquired on chronic drug usage. MDR has been observed in many forms of cancer that include solid tumor and blood cancer. Resistance can be useful for protecting bone marrow when higher dose of chemotherapy is administered by transplanting transformed CD34 cells [(2)].

Although many advances have been taken for its prevention at early stage but cancer cure remain major therapeutic obstacle up to date. Cancer may be treated with radiation, chemotherapy, immunotherapy and hormonal therapy. Most of time systematic chemotherapy remains main therapy for benign or malignant tumors. After treatment with chemotherapy many times the cancer may relapse and lead to death of person. Often during disease progression and on chronic use of above described therapy, multiple drug resistance (MDR) takes place by tumor cells. The MDR may be intrinsic or acquires by tumor cells. Commonly resistance will develop over chronic use and the increased amount of dose required for overcoming this phenomena. But while dose is increased, it also leads to proportionally increase in severity of toxicities. Mechanisms responsible for MDR are altered growth signaling cascade like transdermal growth factor, epidermal growth factor, Wnt/*β*-catenin, hedgehog pathway, mutation of many genes that translated to transporter proteins, altered enzyme expression like DNA repair enzyme, ceramide metabolizing enzyme, cyclooxygenase, metalloproteinase and presence of anti apoptotic factors [(3)]. Many times loss of surface receptor for rugs and loss of transporter (as occur in methotrexate resistance) that transmit the drug inside of cancer cell my play important role in cancer. Once resistance has been developed to one drug, it may possible that other structurally and functionally dissimilar drug can also show cross resistance [(4)].

Recently researcher from University of California, San Diego School of Medicine have discovered an important biomarker molecule named by CD 61 that is responsible for resistance and involved in metastasis of tumor by provide stem cell like property to cancer cells.

2. DIFFERENT MECHANISM INVOLVED IN MULTIPLE DRUG RESISTANCE

2.1. ATP-binding cassette transporters

Living cells possess number of transporter proteins which are located in plasma membrane and functioning for continuous maintenance of normal intracellular and extracellular level of different substances like electrolyte, small molecules like glucose, amino acids.

ATP-binding cassette (ABC) transporters constitutes major transmembrane family involved in ATP hydrolysis dependent translocation process of many endogenous substances, xenobiotics, in DNA repair and in the process of RNA translation [5].Approximately 49 transporters are discovered and are classified into 7 (A-G) families [6]. The various member of this super family includes multiple drug resistance (MDR) gene products like permeability-glycoprotein (P-gp), Multidrug resistance-associated protein (MRP), placenta-specific ATP-binding cassette protein (ABCP), breast cancer resistance protein (BCRP) [3]. The function of ABC transporter not only limited to cancer resistance but also involved some inherited human disease, cystic fibrosis and resistance of antibiotics in infection.

ABC transporter includes following families:

2.1.1. Permeability-glycoprotein

The P-gp is the first ABC transporter identified in human. It is also termed ABCB1 or MDRA or cluster of differentiation 243 (CD243). In the middle of 1970, the correlation between P-gp and drug resistance was established in ovary cell line of Chinese hamster [7]. The pioneer work for understanding the structure and function of P-gp was accomplished in 1976 by research team of Scripps Research Institute and the Texas Tech University Health Sciences Center. Structure of P-gp was determined by x ray crystallography in 2009.

P-gp consists of total 6 transmembrane helices and 2 nucleotide binding domain and has shape of inverted V. The inner boundary made up of variety of hydrophobic amino acid so P-gp can accommodate variety of substrate. P-gp is type of ABC transporter is an important and the best known membrane transporter responsible for MDR. P-gp present at many places of body like cells of kidney, liver, adrenal cortex, brain, intestine, blood-brain barrier and blood-placental barrier, all possesses P-gp [8]. Normally P-gp involved in elimination of harmful substances outside of cell, but same thing responsible for MDR involved in many infection, cancer and psychiatric disease, parasitic disease, AIDS. P-gp also involved in lipid transport, in the secretion

of aldosterone hormone. So the action of P-Glycoprotein is like two edge sword means beneficial and harmful. ABC transporter is glycoprotein that actively efflux the drug from the cells against the concentration gradient at the expense of metabolic energy. The P-gp catch the molecule inside its inverted V shape and open its opposite side close end towards extracellular side while closing the previously open side. In doing so the P-gp ejects the drug molecules outside the cells. It results in prevention of the accumulation in cells of therapeutic concentration of chemo drugs. Strategies for overcoming this problems are development of compounds those are not substrates of efflux pumps, use of agents that inactivate MDR proteins, design of cytostatics characterized by fast cellular uptake, surpassing their mediated efflux, use of compounds competing with the drug for the MDR protein-mediated efflux. Although there are various things responsible for MDR but it is believed that P-gp is major one. The normal cells and cancer cells are differ in much aspect one of that is cancer cells develop lots of P-gp on the surface which ultimately leads to multidrug resistance in course of chemotherapy [9]. After generating P-gp by various tumour cells at their surface, it embraces and ejects many structurally diverse molecules and pushing the patient in tunnel of death by making their therapy fail.

Various substances like lipid, bile pigment, cardiac glycoside digoxin, immunosuppressant drugs, dexamethasone, and chemo drugs like doxorubicin, etoposide, vinblastine and tacrolimus, colchicines, anti viral drugs like protease and non nucleoside reverse transcriptase inhibitor also ejected out from the cell by P-gp.

Experimentally it has been proven in genetically engineer fibroblast cell line that cell deficient of P-gp are more susceptible to many anti cancer agent like anthracycline, etoposide, paclitaxel and vinca alkaloids [10]. One another research also shown that treatment with verapamil, a P-gp inhibitor reverses the resistance nature of DU145 and PC3 cells to doxorubicin [11]. The enhanced expression of ABCA2 and ABCA3 transporters in leukemia linked to resistance to doxorubicin, methotrexate and vinblastine anti cancer drugs compare to normal bone marrow [12]. The P-gp inhibitors involved many drugs like verapamil, azithromycin, amiodarone, reserpine, cyclosporine, captopril.

Classification of P-gp inhibitors

1. First generation- Verapamil, Cyclosporin

2. Second generation- Biricodar, valspodar

3. Third generation- tariquidar, zosuquidar, laniquidar

The first generation drugs have poor efficacy and some toxicity profile so it was not acceptable. Second generation drugs have pharmacokinetic interaction and affecting many other

transporter of the cell other than P-gp. While the third generation drugs are more potent, specific and virtually no any kind of pharmacokinetic drug interaction and interaction with anti cancer drug has been observed [13].

Many P-gp inhibitors has been tried along with chemotherapy but for overcome MDR but due to lack of discrimination between P-gp of normal and cancer cells, many toxicities are arise. Based on enhanced permeability and retention effect, nanopharmaceutical drugs have been developed for specific delivery of drugs to tumor only compare to any other region of the body. The nanotechnology based target found positive result and possible mechanism may be alteration of signaling cascade, increase in drug uptake by cell through endocytosis, altered expression of P-gp and ATP depletion [14].

Some drug like rifampicin found able to induce P-gp gene expression and it may implicated in decreased level of digoxin bioavailability that administered concomitantly [15].

2.2. Resistance to tyrosine kinase targeted therapy

Tyrosine kinases (TK) plays crucial role in growth, proliferation, apoptosis and in formation of new blood vessel [16]. So, researcher found this enzyme as important target for cancer treatment. The enzyme is targeted by monoclonal antibody (Bevacizumab, Panitumumab, Trastuzumab), small molecule tyrosine kinase inhibitor and interfering RNAs. In cancer TK are over expressed that promote dimerization of receptor in the absence of ligand. Therapy with TK inhibitor develops resistance in short time of period. The first mechanism of resistance is occurrence of mutation mostly point mutation. Mutation causes decrease in affinity of inhibitor to TK, change in variety of amino acid surrounding drug binding site and increases the affinity of ATP to TK [17]. The best known example is resistance to Imatinib that is used for chronic myeloid leukemia [18]. Structural evidence indicates that Imatinib not able to fit properly in mutated form of BCR-ABL protein. Other possible mechanisms involved are gene amplification and deletion, altered protein expression and escape by utilization of alternative pathways [16].

2.3. Resistance due to DNA repair enzyme

The cancer therapy involves DNA damaging agents like carboplatin, cisplatin and target cancer cell towards apoptosis. The damage of DNA many times repaired by DNA repair enzyme and cancer cell escape apoptosis. The damage caused by cisplatin repaired by xerodermapigmentosum group E binding factor (XPE-BF) and Excision repair cross-complementing protein (ERCC1) proteins found in higher concentration in resistance cell compare to cisplatin sensitive cell [19].

2.4. Resistance involving ceramide metabolizing enzyme

Ceramide is structural unit of sphingolipid, a sphingomyelin involved in initiation of cell death pathway activated by various chemotherapy, radiation and cytokines, growth factor deprivation and stress [20]. Ceramide synthesized from sphinganine and fatty acid by enzyme ceramide synthase *de novo* and as degradation product from sphingomyelin by the enzyme spingomyelinase. The end of activation of ceramide pathway may be apoptosis [21], proliferation [22], cell cycle arrest and cell differentiation [23]. Ceramide work as second messenger and target many proteins like ceramide-activated protein kinase, atypical protein kinase C, Ceramide activated protein phosphatases and raf-1. Further these proteins activate mitogenactivated protein kinase pathway [24] and stress activated protein kinase/c-JUN N-terminal kinase pathway [25] that responsible for transcription of many gene involved in apoptosis. Etoposide, paclitaxel, vinca alkaloids and anthracycline drugs and cytokines like tumor necrosis alpha (TNF-α), Granulocyte macrophage colony stimulating factor (GM-CSF) has been found to increase Ceramide synthesis through above enzymatic pathway while tamoxifen, mifepristone, ketoconazole and verapamil inhibite glucosylceramide synthase and block the conversion of Ceramide to glucosylceramide by glycosylation [20]. Evidences available for defective Ceramide signaling pathway and resistance of cancer cells to undergo apoptosis after damage induce by radiation in Burkitt's lymphoma [26] and in thymoma cell lines [27]. When synthesis of Ceramide is decreased correspondingly the response to chemotherapy and radiation also reduced and increased cellular Ceramide proportionally increased chemotherapy and radiation response. By targeting Ceramide pathway it may be possible to reverse chemotherapy induced resistance. Many resistance cell lines have enzyme glucosylceramide synthase that form noncytotoxic metabolite glucosylceramide and this molecule may have important role in evade apoptosis [28].

2.5. Resistance due to defective apoptotic pathway

Many damaged cell due to action of chemotherapy and normal cell that had defective or damaged DNA targeted to apoptosis pathway. Transcription factor p53 involve in cell cycle progression and apoptosis. Whenever cell DNA damaged it lead to sudden rise in p53 gene product. The subsequent step is cell cycle arrest and DNA repair or activation of PUMA and Noxa, a bcl-2 family proapoptotic member that push the cell toward apoptosis. By doing so p53 gene product help to eliminate potentially mutated cell and it's transformation to cancer cell. Any cells those are deficient of p53 gene not able to approach apoptosis pathway and that's why resistance arise in chemotherapy treated cancer cells. Oxygen and growth factor deprivation also leads to apoptosis but lack of p53 may interfere with that process [29]. Many human cancers are found with mutation in p53. Mutated p53 not able to repair the cell or target the cell to apoptosis pathway so damaged and unrepaired cell continually divide and it

will later on give resistant progeny that could not be targeted by cytotoxic DNA damaging agent [2].

2.6. Modification of drug target

During the course of therapy, drug target may modified or decrease in concentration that make drug molecule ineffective. Cancer cell are highly mutated cell and it may be possible that protein target may absence due to deletion of gene from cancer cell chromosomes. The hormonal therapy for breast cancer consists of anti-oestrogen tamoxifen that after continue use shown resistance. The resistance cell has been found with loss of estrogen receptor [30]. Many times after treatment with anti cancer drug genetic changes taking place in cancer cells that make expressed protein less susceptible to drug. Although targeted proteins not able to bind with drugs but can able to do carry out its normal function because of stereochemical changes. The result of this change culminates into resistance. Imatinib, a tyrosine kinase inhibitor shows resistance on chronic use in chronic myeloid leukemia. Imatinib cause apoptosis by interference with bcr-abl receptor and ATP interaction, but in few patients single point mutation found in bcr-abl that make imatinib ineffective [31]. The inner environment of tumor is ischemic and hypoxic so it causes less penetration of chemotherapy drug in deep of tumor so it would easy to treat newer small neoplasm compare to advance and larger one.

Some miscellaneous components of MDR include alteration of metabolic enzymes and carrier molecules [32], elevated level of protein kinase C in breast cancer [33] and rise in the level of IL-6 in breast cancer [34], change in glutathione *S*-transferase [35] and topoisomerase II activity [36].

3. Approaches to surmount resistance due to ABC transporter

Many steps have been taken to overcome resistance due to ABC transporter. It includes inhibition of transporter, synthesizing antibody against transporter and blocking molecular pathway responsible for over expression of transporter. Many such agents are synthesized and combine with conventional chemotherapy drugs but results are not satisfactory. There are many reasons for poor efficacy like systemic toxicity, lower bioavailability, effect on more than one target and higher first pass effect [37]. In case of MDR, the higher dose of drug may able to overcome resistance due to dose response relationship. Development of specific monoclonal antibody against cancer cell P-gp may help to overcome resistance. Newer drug analogue that are not substrate for P-gp can be synthesize like DJ-927 [38] and ortataxel [39] for overcome resistance. Nanotechnology based formulation can be developed like anti cancer drug that is substrate for P-gp can be encapsulated with P-gp inhibitors. One already developed drug is TOCOSOL that is combination of paclitaxol and vitamin E along with D-α-tocopherol polyethylene glycol 1000 succinate, a P-gp inhibitor [40]. Synthesize newer chemotherapy drugs that are not at target of P-gp is also one way to overcome resistance. The application of novel

drug delivery system includes liposome, micelles, lipid nanocapsule formulation of anti cancer drug may be good option for combat MDR [9].

4. RECENT ADVANCES IN MDR PREVENTION

Team of Chinese and American researcher found newer approach for Overcoming multidrug resistance in cancer cells by silencing genes with RNA by gene therapy. In this research scientist targeted P-gp by nano formulation [41]. Omega 3 fatty acid by down-regulating cholesterol synthesis and altering detergent resistant membranes composition found useful to overcome chemoresistance in MDR colon cancer cells [42].

5. DISCUSSION

At the present time, Cancer is progressing in dangerous way. Many therapies are available for treatment of cancer but cure rate is very poor unless cancer diagnosed at early stage. MDR is major problem of chemotherapy that is employed for many advance cancer. It may be possible that the subfamily of MDR1 protein responsible for MDR and need to be characterized. If possible, in vitro cell line studies should carry out for determination of resistance prior to in vivo anticancer activity. Many Pharma and biotech company like Biochem pharma, immune, Ingenex, Isis Pharmaceuticals and Titan Pharmaceuticals are under way of development of P-gp resistance molecules. Incel, a new molecule has been found to increase in concentration of chemotherapy drug in cancer cells and make cancer cells more sensitive by affecting MDR1. It may be possible that some drug affect and reverse resistance in vitro but when administered in vivo that is not effective like toremifene. The reason may include degradation or conjugation with some biomolecule makes them ineffective in vivo. Although many molecules kick out from tumor cell by ABC transporter some drug like olivacine derivative shown good anticancer activity both in vitro and in vivo in those cancer cells with phenotype of MDR1 gene. Olivacine rapidly accumulate tumor cell by fast uptake and bypass the action of P-gp. It will be of great importance to find out correlation between ABC transporter gene and other genes that are involved in cancer like p53 for better prognosis of cancer. Targeting MDR1 gene promoter with anti sense has shown increasing in efficacy of vinblastine in resistant leukemia cells that is defined as transcriptional decoys [43]. The future may come with many strategies to overcome resistance and us able to solve a major problem of Chemotherapy and antibiotic therapy.

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