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Resistance to Anticancer Agents: Recent Trends

Ahmed M. Kabel[1,2,*], Maaly A. Abd Elmaaboud[2]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
[2]Pharmacology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
*Corresponding author: ahmed.kabal@med.tanta.edu.eg

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Abstract Resistance to the anticancer agents is a complex process that mainly results from alteration in the targets of the chemotherapeutic agents. Mechanisms that underlie resistance to the anticancer agents include inactivation of the drug, inhibition of cellular apoptosis, changes in the metabolic pathways of the drug, increased expression of the efflux proteins and enhancement of DNA repair and gene amplification. Several strategies were developed to overcome this resistance. The use of the combination chemotherapy is the best option for drug resistant types of cancer. This review throws light on resistance of cancer cells to the chemotherapeutic agents in view of the recent trends.

Keywords: *cancer, multi-drug resistance, anticancer agents, management*

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1. Introduction

Cancer is a group of disorders characterized by loss of control on cell growth and differentiation [1]. The anticancer drugs act by different mechanisms that regulate different phases of cell cycle leading to inhibition of growth of cancer cells. However, development of drug resistance by cancer cells is the main cause of failure of cancer therapy [2]. Drug resistance is a phenomenon that occurs when a disease becomes tolerant to pharmaceutical treatments. Resistance to chemotherapeutic agents occurs when cancer cells develop molecular alterations that make them insensitive to a certain drug. In some instances, cancer cells may adapt to the drug while it is being administered, acquiring molecular changes that render them resistant to its effects [3].

There are many mechanisms that promote resistance of cancer cells to chemotherapy, including interference with drug penetration, activation of the efflux mechanisms, drug inactivation, mutations in the target proteins, decreased the affinity for the drug, development of alternative biochemical pathways, DNA damage repair, inhibition of cell death, and the epithelial-mesenchymal transition [2]. The increased prevalence of multi-drug resistant cancers necessitates exploration of the possible mechanisms and searching for ways of overcoming of this resistance [4]. The aim of this review is to throw light on resistance of cancer cells to the chemotherapeutic agents in view of the recent trends regarding its prevalence, etiology, mechanisms, diagnosis and possible lines of management.

2. Etiology of Resistance to the Anticancer Drugs

2.1. Decreased Absorption of the Drugs

Absorption of the anticancer drugs into cancer cells occurs either by passive transfer, facilitated diffusion or activate transport [2]. The anticancer agents enter the cells along the concentration gradient by ABC transporter molecules. Cancer cells may decrease absorption of the anticancer drugs by reducing the tendency to binding of the drugs to these transporters, decreasing the numbers of the transporters or by mutation of the transporters themselves [5]. For example, resistance of cancer cells to methotrexate may be mediated via mutation in the human folate carrier's gene in patients with acute lymphoblastic leukemia [6].

2.2. Increased Release of the Anticancer Drugs outside the Cells

ATP-binding cassette (ABC) transporters are ATP-dependent transporters that are involved in the transport of the nutrients and other molecules across the cell membrane [7]. The ABC family has three members, including P-glycoprotein, multi-drug Resistance-associated Protein 1 and breast cancer resistance proteins. P-glycoprotein is a multidrug membrane transporter that normally can bind to a wide range of chemotherapeutic agents [8]. When these agents bind to P-glycoprotein, ATP is hydrolyzed and the structure of P-glycoprotein is altered

leading to extrusion of the drug to the extracellular space. This is the mechanism responsible for resistance of cancer cells to doxorubicin, taxanes and vinblastine [2].

2.3. Inactivation of the Anticancer Agents

Cancer cells may become resistant to the anticancer drugs by reducing the activity of these drugs [9]. For example, cytarabine which is used for treatment of acute myeloid leukemia needs multiple phosphorylations to be converted to cytarabine triphosphate which has high toxicity to cancer cells. Mutations in the proteins and enzymes that are involved in these phosphorylation reactions decrease the activity of cytarabine in cancer treatment [10]. Another example of inhibition of the activity of anti-cancer drugs is glutathione S-transferase enzyme which increases resistance of cancer cells to chemotherapy by detoxification of the anti-cancer agents [11]. Increased expression of glutathione S-transferase in cancer cells reduces the cytotoxic effect of a wide range of the anticancer drugs and increases resistance of cancer cells to apoptosis [12].

2.4. Inhibition of Apoptosis

Apoptosis is an important cellular event that regulates cell death. Several proteins are involved in the intrinsic and extrinsic pathways of apoptosis including B-cell lymphoma 2 (BCL-2) family proteins, caspase-3, caspase-9 and Akt [13]. It was observed that in multi-drug resistant cancers, there was increased expression of the antiapoptotic proteins such as BCL-2 and Akt and increased activity of the down-stream transcription modulators such as nuclear factor kappa B [14]. Moreover, the cancer cells may decrease the expression of c-Jun N-terminal kinases (JNK) with subsequent inhibition of apoptosis, which is frequently encountered in resistance to cisplatin [15].

2.5. Alteration of Metabolism of the Anticancer Drugs

Enzymatic metabolism of the anticancer agents is responsible for determination of the effective drug concentration inside cancer cells [2]. Cytochrome P450 enzyme system is one of the enzymes responsible for phase I metabolism of some anticancer drugs. Cases of breast cancer resistant to docetaxel may be associated with increased activity of cytochrome P450 leading to docetaxel inactivation [16]. Also, resistance of cancer cells to alkylating agents may be attributed to increased activity of the enzymes responsible for phase II reactions leading to loss of the electrophilic toxicity of these agents [17].

2.6. Alteration of Drug Targets

Mutations or modifications of the expression levels of the molecular targets of the drug have a direct influence on its efficacy [2]. For example, topoisomerase II, which is an enzyme that prevents DNA from super- or under-coiling, represents an important target for some anticancer agents [18]. The anticancer drugs stabilize the interaction between DNA and topoisomerase II resulting in serious DNA damage, inhibition of DNA replication, and arrest of mitosis. Cancer cells may show resistance to these anticancer agents through mutations in the expression of topoisomerase II gene [19].

2.7. DNA Damage Repair

Most chemotherapeutic agents may directly or indirectly damage DNA resulting in death of cancer cells [20]. However, some cancer cells may develop DNA damage response mechanisms rendering these cells resistant to chemotherapy [21]. For example, resistance of cancer cells to platinum-containing cytotoxic drugs often develop due to activation of DNA repair mechanisms such as homologous recombination and nucleotide excision repair. Inhibition of these repair mechanisms by combination chemotherapy often sensitizes cancer cells to the cytotoxic effects of the chemotherapeutic agents [22].

2.8. Epithelial-mesenchymal Transition and Metastasis

Epithelial to mesenchymal transition (EMT) is a mechanism that facilitates spread of solid tumors and formation of distant metastasis. This process involves the occurrence of changes in the cancer epithelial cells and the stromal cells associated with angiogenesis [23]. During EMT, cancer cells increase the expression of cell adhesion receptors that enhance cell motility and decrease cell-to-cell attachment. Also, there is increased expression of metalloproteases on the tumor surface which facilitate cell motility and promote metastasis [24]. Resistance of cancer cells to chemotherapeutic agents may develop during the signaling processes of differentiation, which are essential for EMT [2]. For example, cases with refractory colon cancer were associated with increased expression of transforming growth factor β (TGF-β) which is required for EMT rendering them resistant to chemotherapy [25].

2.9. Gene Amplification

Gene amplification means increase in the numbers of target genes in some cancer cells especially in cases of leukemia and lymphoma [26]. For example, resistance to methotrexate in some types of leukemia is mediated via providing multiple copies of the dihydrofolate reductase gene which target the site of action of methotrexate. This confers massive resistance to methotrexate making it even entirely ineffective on cancer cells [27].

2.10. Epigenetic Alteration

Epigenetic alteration is a heritable change that does not affect the DNA sequence but results in a change in gene expression [28]. The mechanisms of epigenetic alterations include DNA methylation and alteration of histones. These mechanisms lead to alteration of the structure and composition of chromatin which in turn will affect the gene expression [29]. For example, DNA methylation decreases the expression of the tumor suppressor genes associated with increased expression of the oncogenes

[30]. Also, the epigenetic alteration may affect the DNA repair mechanisms which may antagonize the effects of a wide variety of the anticancer drugs on DNA [2]. Demethylation of the promoter oncogenes and recovery of the mismatch repair mechanisms causes the cells of colorectal cancer to be sensitive to fluorouracil. Accordingly, the combination of epigenetic and conventional chemotherapeutic agents are effective in treatment of resistant malignancies [31].

3. The Effects of Resistance to the Anticancer Drugs

Resistance to anticancer drugs represents a major impediment in medical oncology. This resistance may appear prior to or as a result of cancer therapy [2]. The most important complication of drug resistance is that development of resistance to one drug may lead to resistance to other drugs [32]. For example, loss of a drug transporter may lead to resistance to other compounds that utilize it. Also, elevation of ABC transporters resulting from one drug may have a direct impact on the efficacy of many other compounds [33]. An additional obstacle is that resistance of cancer cells to a certain chemotherapeutic agent may necessitate increase in the dose of this agent which may have serious adverse effects on the normal tissues and organs [2]. Furthermore, the presence of similarities between drug-resistant and metastatic cancer cells in terms of resistance to apoptosis may increase the morbidity and mortality rates [34].

4. Diagnosis of Resistance to the Anticancer Drugs

Drug resistance represents a major problem that is responsible for failure of chemotherapy to cure the majority of cancer patients [4]. About 50% of patients with cancer have resistance to chemotherapeutic agents even before starting drug therapy and about 50% of the remaining cases may develop resistance during the course of treatment [35]. All efforts to overcome resistance to chemotherapy should focus on early diagnosis of this resistance to plan effective measures to overcome this resistance. There are numerous methods for diagnosis of anticancer drug resistance including cancer biomarker tests, fresh tumor cell culture assays, and positron emission tomography tests [36].

5. Management of Resistance to the Anticancer Drugs

The use of combination chemotherapy represents the most effective measure to overcome cancer drug resistance [37]. The rationale for combination chemotherapy is to use drugs that act by different mechanisms, thereby reducing the possibility of development of resistant cancer cells [38]. For some types of cancers, the best strategy of management is a combination of surgery, radiotherapy and chemotherapy. Radiation therapy or chemotherapy may be given before surgery to decrease the size of the tumor, thereby increasing the possibility of complete surgical removal. Radiation therapy and low-dose chemotherapy may be used after surgery to destroy any remaining cancer cells and reduce the possibility of recurrence [39]. Combination chemotherapy may be a valuable option for patients with advanced carcinoma that are not fit for surgery or radiation therapy [40].

6. Conclusion

Cancer cells with a high proliferation rate are genetically unstable, making them potential candidates to develop resistance to anticancer agents. The cancer drug resistance is a complex phenomenon that involves a wide range of different pathophysiologic mechanisms. Therefore, the combination therapy is the best option for refractory types of cancer. Further research is vitally needed to discover promising strategies for amelioration of this serious medical problem.

Conflict of Interest

The authors had no conflict of interest to declare.

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